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Models of Cell Differentiation in Conidial Fungi

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INTRODUCTION

Conidia are asexual reproductive propagules produced by a large group of economically, medically, and ecologically important microbes collectively referred to as the conidial fungi (90). These are the fungi from which many industrial products are derived, such as citric acid, gallic acid, gluconic acid, penicillin, and griseofulvin (165). A large percentage of the important fungal parasites of plants (121, 133), food spoilage and textile-degrading microorganisms (360), and most of those fungi causing mycoses in animals (345) are members of this group. Examples of conidial fungi include *Septoria nodorum*, causative agent of glume blotch of wheat which has led to crop losses of up to 50% in Europe (315); *Aspergillus flavus*, the primary source of aflatoxins and the microorganism largely responsible for birth of the field of mycotoxicology (325); and *Coccidioides immitis*, a primary pathogen of humans and other animals causing San Joaquin fever (100, 387). The typical vegetative growth forms of these microfungi are represented by septate hyphae or yeast cells or both. The presence of cross walls, or septa, in the filamentous phase of all conidial fungi is evidence for their relationship to higher fungal taxa and distinguishes them morphologically from the lower, aseptate hyphal forms such as the water molds and Zygomycetes (432). The majority of conidial fungi (>15,000 species; 3) have no known sexual state. These are referred to as the Fungi Imperfecti and accommodated in the subdivision Deuteromycotina (4). The latter is further separated into three form-classes, Blastomycetes, Coelomycetes, and Hyphomycetes (432). The term form-class is used since the classification does not necessarily reflect phylogenetic relationships but is rather a convenient scheme for assembling taxa based primarily on morphological similarities. Unfortunately, this classificatory system has often led to confusion, especially for those genera such as *Candida* which includes many species with divergent phylogenies (2, 268, 297, 344). The Blastomycetes include the yeasts or yeast-like fungi in which the hyphal mass (mycelium) is lacking or not well developed (261, 280). The Coelomycetes give rise to conidia from modified hyphae (conidiogenous cells) which are formed within a cavity lined by fungal tissue, host tissue, or a combination of both (400). The Hyphomycetes produce conidia from aggregated or separate conidiogenous cells borne on the exterior face of substrates and not enclosed by additional fungal or host tissue (61). This last form-class also includes the Mycelia Sterilia (Agonomycetes; 3), in which conidiation does not occur and the fungus reproduces asexually by hyphal growth and fragmentation. The conidial fungi, therefore, largely represent an assemblage of orphans, the taxonomy of which is a formidable challenge even for the most experienced mycologists (249). On the other hand, they do reveal morphological, developmental, and biochemical similarities to the asexual states, or anamorphs (202), of meiospore-producing septate fungi: the Ascomycetes and Basidiomycetes (248). The Deuteromycetes are generally considered to be anamorphs of Ascomycetes, and more rarely of Basidiomycetes, whose sexual states, or teleomorphs, have become permanently separated, temporarily disconnected, and are not recognized or never existed in the first place (400). The absence of meiotic division during the life cycle of conidial fungi has not restricted their adaptive radiation. Genetic variation resulting from parasexual recombination in the Deuteromycetes (196, 328, 354) apparently provides for

sufficient heterogeneity in their gene pool to more than compensate for the absence of meiotic divisions.

The focus of this review is on developmental aspects of the conidial fungi and the many potential models of eucaryotic cell differentiation inherent in this group of microorganisms. Examples of ontogeny are chosen primarily from the Hyphomycetes, with some reference to developmental processes in blastomycetous and coelomycetous fungi. For detailed discussions of yeast morphogenesis and the interconversion of yeast and hyphal phases (i.e., dimorphism), readers are directed to several recent reviews (279, 320, 362, 383, 384, 390, 402).

ONTOGENY AND CLASSIFICATION

Early studies of ontogeny in the conidial fungi were performed by workers whose primary interest was the systematics of the Deuteromycetes (223, 233, 290, 291, 421, 423). The common goal of these investigators was the provision of a more reliable classification of the Fungi Imperfecti than the scheme originally formulated by Saccardo (357), which was based almost entirely on characters of mature morphology, such as color, shape, and septation of conidia. Taxonomists were particularly frustrated with the inconsistencies of the Saccardoan classification and took the initiative by proposing to arrange members of the Hyphomycetes into sections wherein the kinds of reproductive cell development and structure were the primary differentiating characters. The ontogeny of conidia and the sometimes elaborately differentiated cells from which conidia are formed (i.e., conidiogenous cells) were carefully examined (Fig. 1). Hughes (223) described eight distinct modes of development which became the basis of an experimental classification (395). The author proposed that "there are only a limited number of methods whereby conidia can develop from other cells and that morphologically related imperfect states will only be brought together when the precise methods of conidium origin take first place in the delimitation of the major groupings." It would appear from the extensive applications of Hughes' concepts to classificatory schemes of Hyphomycetes (19, 61, 108, 131, 132, 394, 395), Coelomycetes (315, 400), and even yeasts and yeastlike fungi (419, 420), that a panacea for the taxonomic ills of conidial fungi had been provided. Unfortunately, such aspirations have not been realized since many taxonomic problems persisted even after concerted efforts were made to apply developmental characters to classifications of the Fungi Imperfecti (283). For example, an increasing number of pleomorphic forms have been described which cannot be accommodated in any single developmental category of Hughes' (231), or subsequently published schemes (60, 426, 437, 461). Anamorphs of a single teleomorph (e.g., conidial states of *Venturia*) may demonstrate different asexual reproductive processes (284), which in turn may lead to confusion in classifications of both asexual (anamorphic) and sexual (teleomorphic) states of such fungi. Even more problematic from the standpoint of applying ontogenetic characters to a classification of conidial fungi is the recognition in a few experimental species that simple mutations or even environmental alterations may result in conversion of one mode of conidial development to another in the same individual (65, 346, 410, 411, 418, 424, 459, 460). Confusion has also arisen over terminology, which at the outset was intentionally flexible rather than based on rigid definitions (247), but ultimately generated heated debates over semantic details. These early developmental studies, nevertheless, yielded an encyclopedia of data on the different modes of conidium and conidiogenous cell ontogeny. Modifications of Hughes' (223) original list of developmental categories were necessary as the results of many new investigations of conidium ontogeny were made available. A current scheme is outlined in Fig. 1 (95, 96). The two principal types of conidium ontogeny are referred to as "blastic" and "thallic" development. Blastic conidia differentiate apically or laterally from a fertile hypha by the blowing out and de novo growth of part of the hyphal element and are delimited from the parent hypha by a basal septum (Fig. 1A and B). Blastic conidia commonly secede from their parent hypha by the centripetal splitting of this same basal septum, a process referred to as shizolysis (224, 225). Certain cytological aspects of this developmental process are comparable to daughter cell formation and secession in budding yeasts (91, 96). Thallic development occurs by conversion of an entire segment of a fertile hypha into a single, terminal or intercalary conidium (holothallic conidia; Fig. 1C and D) or by conversion and disarticulation of a hyphal segment into several (arthric) conidia (Fig. 1E to G). Formation of thallic conidia usually involves some enlargement and secondary wall growth but is morphogenetically distinct from the de novo growth of blastic conidia. Terminal, holothallic conidia usually secede from the parent hypha by autolysis of the cell adjacent to and below the basal septum of the newly formed conidium (Fig. 1D). This process of conidial secession has been termed rhexolysis (225). Disarticulation of fertile hyphae during thallic-arthric development may occur by shizolysis (Fig. 1E) or rhexolysis (Fig. 1G).

The fertile hyphae, which give rise to both blastic and thallic conidia, are delimited as conidiogenous cells and differentiate into a range of morphologically distinct forms (Fig. 1H to T). The different kinds of conidiogenous cells are categorized on the basis of their specific modes of development. A determinate conidiogenous cell (Fig. 1H) ceases extension growth at or before the onset of blastic or holothallic conidium formation, respectively, and does not resume extension growth during or between the formation of successive conidia (95). An ampulla is the swollen, fertile apex of a conidiogenous cell which may give rise to a botryose cluster of blastic conidia (Fig. 1I) (73, 253). Sympodial development occurs by a succession of proliferations of the conidiogenous cell just behind and at alternate sides of each new fertile apex, usually resulting in a geniculate cell configuration. Either blastic (Fig. 1J) (251) or thallic (Fig. 1K) (76, 246) conidia may be formed at the apices of such conidiogenous cells. The phialide gives rise to a succession of blastic conidia through a rupture in its outer wall (Fig. 1L). The conidia may collect in droplets or adhere in chains. The youngest conidium is always closest to the fertile apex of the phialide (i.e., basipetal development). The fertile cell apparently does not change in length during formation of successive conidia (86). The annellide also gives rise to a basipetal succession of blastic conidia except that the conidiogenous cell visibly elongates after delimitation of each conidium (Fig. 1M). This developmental process gives rise to a series of ringlike wall scars (annellations) at the conidiogenous cell apex, each scar representing the site where conidial secession (schizolysis) and proliferation of the fertile cell had occurred (87, 222). Such a mechanism of proliferation of each new apex of the conidiogenous cell through the previous apex is referred to as percurrent and is not restricted to the annellidic mode of development. For example, certain phialides (Fig. 1N) and ampullate conidiogenous cells (see Fig. 1O) also demonstrate percurrent proliferations. Like phialides and annellides, retrogressive

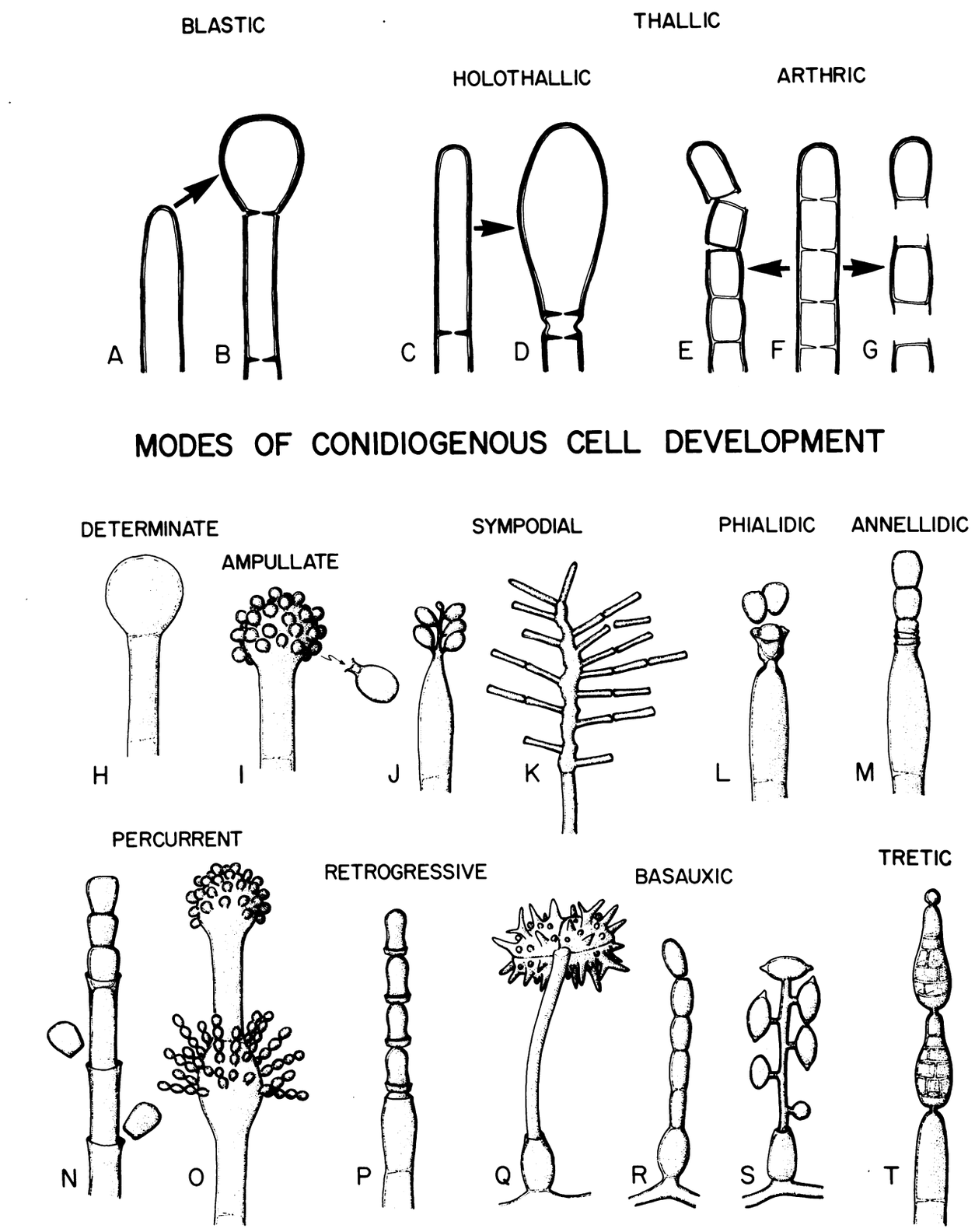


FIG. 1. Diagrammatic summary of different modes of conidial and conidiogenous cell development (after reference 95). Representative genera used to illustrate modes of conidiogenous cell development include the following: *Humicola* (H; determinate), *Gonatobotrys* (I; ampullate), *Tritirachium* (J; sympodial), *Sympodiella* (K; symbodial), *Phialophora* (L; phialidic), *Scopulariopsis* (M; annellidic), *Catenularia* (N; percurrent), *Gonatobotryum* (O; percurrent), *Cladobotryum* (P; retrogressive), *Spegazzinia* (Q; basauxic), anamorph of *Erysiphe* (R; basauxic), *Arthrinium* (S; basauxic), and *Alternaria* (T; tretic).

conidiogenous cells give rise to a basipetal succession of blastic conidia but, in this case, the fertile cell gradually shortens as each newly formed conidium secedes and carries with it part of the original outer, fertile cell wall (Fig. 1P) (89). A more detailed comparison of the phialidic, annellidic, and retrogressive modes of development is presented below in the discussion of septation and secession mechanisms. Basauxic development is demonstrated by those conidiogenous cells in which elongation occurs at a basal growing point (i.e., intercalary growth) after formation of a single, terminal blastic conidium at its apex (Fig. 1O) (75). Continuous or successive periods of intercalary growth at the base of the conidiogenous cell combined with the formation of multiple blastic conidia (Fig. 1R and S, respectively) represent variations in the basauxic mode of development. Finally, tretic (porogenous) (95) development is characterized by the presence of a narrow but distinct channel through the thick conidiogenous cell wall at the junction between the fertile cell and the base of the blastic conidium (Fig. 1T). The channel first appears during conidium initiation, persists throughout conidium development, and is then sealed when the conidium secedes, leaving a corresponding pore on the surface of the conidiogenous cell (72, 131).

HYPHAL TIP GROWTH AND CONIDIUM INITIATION

Concepts of Hyphal Morphogenesis

Just as the key to hyphal growth lies at the tip (160), comprehension of blastic and thallic conidium initiation is suggested to be linked to pivotal events which occur at the hyphal tip and lead to the formation of one or more swollen propagules (Fig. 1A to G) (96). Extension growth occurs at the apical dome of the filament, primarily as a result of transport, accumulation, and fusion of cytoplasmic vesicles with the plasmalemma and subsequent intussusception of new wall material (21, 22, 160, 170). Improved methods of cell preservation for ultrastructural investigations, such as freeze-substitution (212, 218), combined with high-voltage electron microscopy (216) have been particularly helpful in formulating current hypotheses of the mechanism of hyphal elongation. The diagrammatic interpretation of hyphal tip fine structure presented in Fig. 2 is derived from these and earlier electron microscopic studies (78). Hyphal tips of septate fungi are characterized by the presence of a dense cluster of vesicles, both macro- and microvesicles, and the exclusion of almost all other organelles including nuclei, mitochondria, endoplasmic reticulum, and ribosomes (171). The majority of microvesicles at the hyphal apex occupy a central region within the cluster of macrovesicles (Fig. 2). High-voltage electron microscopic analyses of serial sections have revealed that microvesicles reside in a meshwork of microfilaments within a lumen surrounded by macrovesicles (Fig. 2, insert) (216). The nature of fungal microfilaments is still unknown, but results of investigations of other eucaryotic microbes suggest that actin, myosin, and associated proteins are probable constituents (160). Allen et al. (6) have demonstrated that treatment of *Neurospora crassa* hyphae with cytochalasin A results in dispersion of vesicles at the hyphal tip and formation of apically swollen or spatulate hyphae. It appears that maintenance of an organized cluster of macro- and microvesicles at the tip, which was originally referred to as the Spitzenkörper (apical body) based on light-microscopic observations (151), is essential for normal polarized growth of the hypha. If hyphal tip growth is arrested, the Spitzenkörper disappears, and when the direction of elongation is altered, a shift in position of the apical cluster of vesicles preempts any visible change in growth pattern (151, 152, 160). In freeze-substituted preparations of *Fusarium acuminatum* hyphae (218), the macrovesicles are spherical, measure 70 to 90 nm in diameter, and are revealed as light- and dark-stained structures by electron microscopy. Microvesicles are approximately 30 nm in diameter, appear hexagonal in cross section, and are typically coated with radiating spikes of electron-dense material. Some microvesicles are also coated with a filamentous layer. The authors referred to these previously undescribed organelles as filasomes (Fig. 2).

Investigations of the enzymology of hyphal growth in a wide range of fungi have provided evidence that the deposition of polysaccharides (e.g., chitin and glucan) in growing hyphae occurs mainly in the apical 1 μm (26, 147, 156, 160). Good evidence is also available that polymerization of chitin microfibrils occurs exclusively outside the plasmalemma and the biosynthesis of this cell wall product is controlled by the activity of chitin synthetase present in the cell membrane (54, 56, 135, 159, 415). The zymogenic form of chitin synthetase has been found localized in discrete particles termed chitosomes, which are 40 to 70 nm in diameter and surrounded by a shell or unit membrane-like outer layer (22, 24). Chitosomes closely resemble at least some of the microvesicles in the hyphal tip (22, 28, 160). The microvesicular core of filasomes is strikingly similar to chitosomes. Its filamentous matrix, however, is not composed of chitin microfibrils (216). Chitosomes have been isolated from cells of diverse fungi, their constituent enzyme has been activated by proteases, and they have been shown to be capable of forming chitin microfibrils when incubated with the substrate uridine 5′-diphosphate-*N*-acetylglucosamime (25). Bartnicki-Garcia and co-workers (28) have proposed that the chitosome plays "a key role in cell wall construction, and hence, morphogenesis: it is the microvesicular vehicle by which the cell delivers, to specific sites on the cell surface, individual, organized packets of chitin synthetase, each packet being responsible for synthesis of one microfibril." These same authors (28) suggested that chitosomes may arise from endoplasmic reticulum (dictyosomal cisternae?) or multivesicular bodies, organelles which have been found associated with hexagonal microvesicles in freeze-substituted hyphae (Fig. 2) (212, 216). They also speculated that chitosomes may form independently by a process of self-assembly of subunits which occur freely in the cytoplasm or within multivesicular bodies. The chitosomes are presumed to be capable of fusion with the plasmalemma or pass through the membrane (exocytosis?) at specific sites, such as the hyphal tip, and subsequently initiate chitin microfibrillogenesis (Fig. 2, insert) (28). The authors have argued that evidence presented by other workers indicating that the plasmalemma is the main site where chitin synthetase (zymogenic and activated forms) resides in yeasts and other fungi (54, 56, 125) is possibly an artifact arising from the preparation of plasma membrane from protoplasts (24). Bartnicki-Garcia and co-workers (24) have pointed out that the preparation of protoplasts is a slow process that not only disrupts the growth of the cells, but causes a number of metabolic changes. In particular, the "cellular machinery for chitin synthesis seems to be . . . sensitive to the manipulations used in making protoplasts." The high levels of chitin synthetase reported for plasma membrane fractions may result from the precipitous discharge of vesicles, including chitosomes, against the plasmalemma during protoplast formation (24).

Elaboration of a wall at the hyphal tip composed of

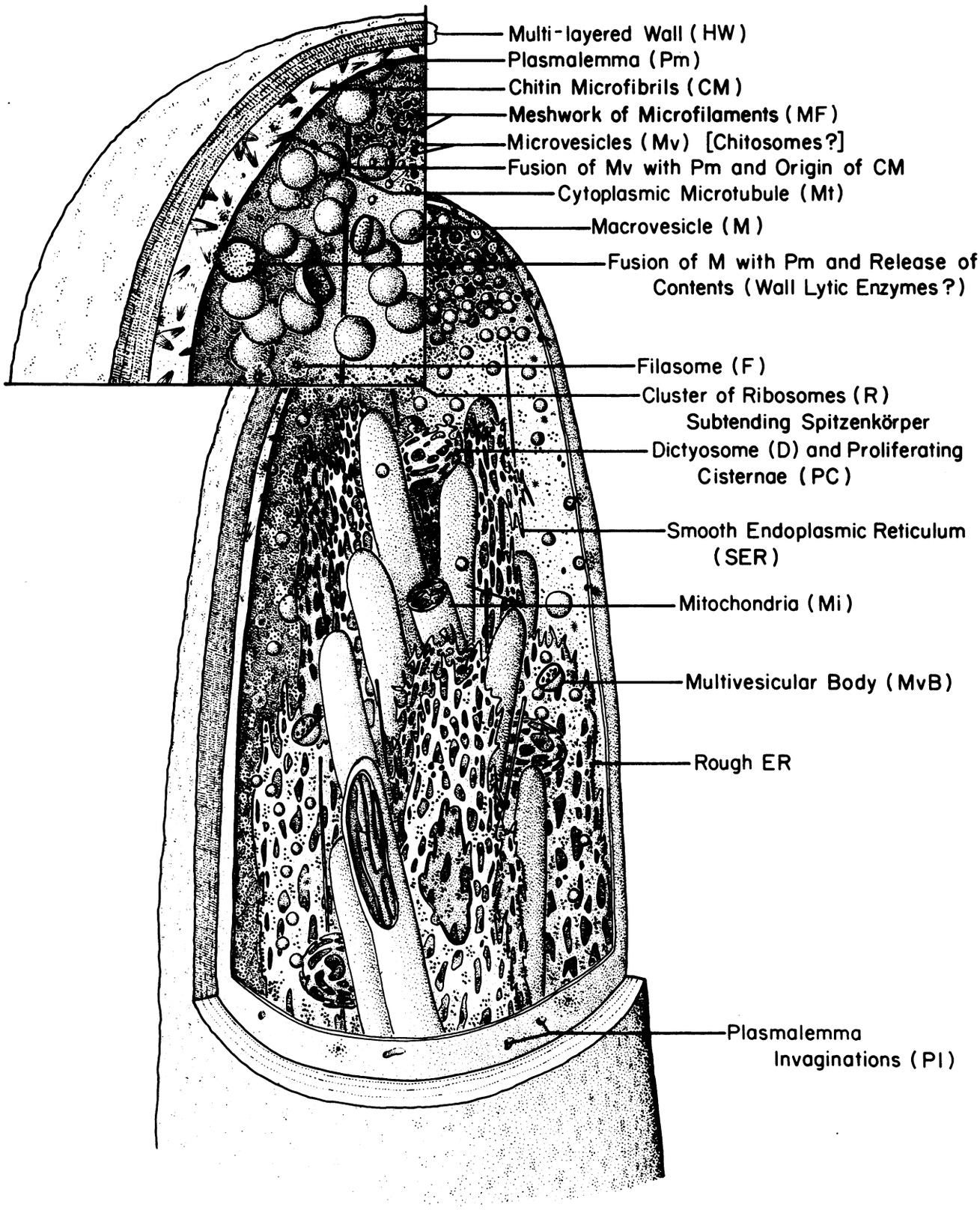


FIG. 2. Diagrammatic interpretation of cytological aspects of a hyphal tip.

interdigitated microfibrils would logically tend to increase wall rigidity and thereby restrict polarized extension growth. Fungal morphogeneticists are still wrestling with this apparent contradiction, but most agree that differentiating fungal walls also contain lytic enzymes which are responsible for maintaining wall plasticity by modifying the microfibrillar matrix for expansion and insertion of newly synthesized polymeric material (21, 157, 355). Results of investigations of wall biosynthesis in budding yeast cells support this concept (56). Cell lysis has been demonstrated when yeast cells are treated with aculeacin A, a cell wall-active antibiotic which inhibits the synthesis of β-1,3-glucan and interferes to some extent with the synthesis of mannan (40, 302, 303, 455). β-1,3-Glucan in certain yeasts is considered to provide structural support and thereby contribute to cell shape (141, 164). In other words, wall growth is arrested but cell growth continues because of the presence of lytic enzymes capable of wall dissolution (56). Some evidence is also available for the localization of lytic enzymes in the wall of fungal hyphae, including β-(1,3)-glucanase (263), *N*-acetyl-β-D-glucosaminidase, and chitinase (160, 211). These last two "morphogenetic enzymes" have been suggested by Gooday (160) to function in a regulatory role in the "*N*-acetylglucosamine cycle by locally degrading the preexisting chitin microfibrils to *N*,*N*′-diacetylchitobiose and *N*-acetylglucosamine, both of which would then locally activate chitin synthetase" (e.g., zymogenic form of chitin synthetase delivered to plasmalemma by chitosomes), "resulting in the insertion of new chitin microfibrils and wall expansion, before then being recycled to provide further substrate UDP-*N*-acetylglucosamine for further chitin synthesis." A balance between wall synthesis and lysis could maintain an orderly process of extension growth at the hyphal tip. Although little information is yet available on the details of such a regulatory mechanism, it appears that hyphal wall material shows marked reduction in susceptibility to autolytic enzyme activity soon after it is deposited outside the plasmalemma (i.e., subapical region; 305, 326, 327, 332). On this basis, plasticization of the hyphal wall would occur primarily at the apical dome. Localization of lytic enzyme activity may also be mediated by macrovesicles. The latter are probably derived from proliferating dictyosomal cisternae (Fig. 2) (152, 160, 216), may be capable of compartmentalizing wall lytic enzymes or their precursors which are synthesized within the dictyosomes (146–149, 158, 208–210, 313, 318), and appear to be directed to the hyphal tip where they can fuse with the plasma membrane (160). The contents of the macrovesicles are thereby delivered to the site of wall biosynthesis, and new membrane is simultaneously contributed to the plasmalemma as extension growth proceeds (Fig. 2, insert).

An important aspect of both macro- and microvesicular involvement in polarized growth is the mechanism(s) which regulates their movement from subapical to tip region (105). In an earlier review of the regulation of cell wall biosynthesis in yeasts, Cabib et al. (56) stated: "Nowhere is our ignorance more complete than in the area of those directional systems that carry with great precision vesicles and other organelles to selected targets in the cell. This is certainly one of the most important, if difficult, topics for future research." Abundant microtubules are found in the subapical region of hyphae (154) and occasionally are observed extending through the cluster of apical vesicles to the plasmalemma (Fig. 2, insert) (212, 216). Good experimental evidence is available, using certain antitubulin and antifungal agents, such as vincristine, griseofulvin, and nocodazole, that microtubules are at least involved in movement of mitochondria, nuclei, and lipid droplets in fungal hyphae (Fig. 2) (115, 160, 353). Using the systemic fungicide methyl benzimidazole-2-yl carbamate, which binds directly to tubulin, Howard and Aist (217, 219) demonstrated the disappearance of cytoplasmic microtubules, concomitant disorganization of the Spitzenkörper, and displacement of mitochondria at the hyphal tip. It appears that cytoplasmic microtubules play an important role in secretory vesicle and other organelle movement between the subapical and apical regions of hyphae. In addition, Gooday (160) has proposed that a bioelectrical current may be the work force for organelle movement, acting either electrophoretically on vesicles or via an electro-osmotic mass flow. Ionic currents also maintain directional flow into the tip and, therefore, can perform work as well as provide vectorial information (21, 183, 240, 243). Reiss and Herth (341, 342) investigated polarized growth of pollen tubes produced by *Lilium longiflorum* and indicated that a Ca^{2+} gradient is essential for tip elongation. If this gradient is disturbed by application of a cationophore (e.g., X-537A), extension growth is arrested, the apex swells, and the apical wall thickens. A Ca^{2+} gradient has also been demonstrated in fungal hyphae and suggested to play a role in regulating polarized growth (184, 241). Turian and Perez (Proc. 13th Int. Congr. Microbiol., p. 172, 1983) proposed that subapical mitochondria present in elongating conidial germ tubes of *N. crassa* are involved in "sequestration" and "pumping out" of Ca^{2+}, processes which may be regulated by calmodulin. The authors reported that anticalmodulin agents, such as chlorpromazin and penfluridol, disturbed the polarity of growth and resulted in widened, clublike apices. Although a Ca^{2+} gradient may be significant for tip growth, other ionic balances are probably also critical in establishing a gradient for vesicle movement (341, 342). Harold and Harold (184) have provided experimental evidence that proton movements in rhizoids of the water mold *Blastocladiella emersonii* are related to orientation of growth. Galpin and Jennings (145) have proposed that K^+, Na^+, and adenosine triphosphatase are involved in establishing and maintaining an ionic gradient in the hyphae of the marine fungus *Dendryphiella salina*. The technique of energy-dispersive X-ray analysis was used to determine relative concentrations of ions in the tip and subapical regions (146). The authors demonstrated a much higher concentration of Na^+ than K^+ at the tip and the converse in the region 1 to 50 μm behind the tip. Bearing in mind that *D. salina* is a marine fungus which may, unlike terrestrial fungi, maintain a high Na^+ content in its cytoplasm for osmoregulatory purposes, Jennings (243) proposed that membrane-associated adenosine triphosphatase activities in the subapical regions drive an internal potassium current, with a resultant "standing-flow osmotic gradient of water" toward the apex (160).

Blastic Development

The relevance of such movement and distribution of organelles within the hyphal apex to a discussion of conidium initiation will become evident as the focus now shifts from hyphal elongation to blastic conidium formation (Fig. 1A and B and 3). Time-lapse photomicrographic analyses of blastic conidiogenesis conducted on a wide range of species grown in our specially designed culture chamber (84) have indicated that the conical-shaped tip of the fertile hypha slowly "blows out" to form the conidium initial over a 15- to 60-minute period (Fig. 4 and 5) (89, 95). As previously

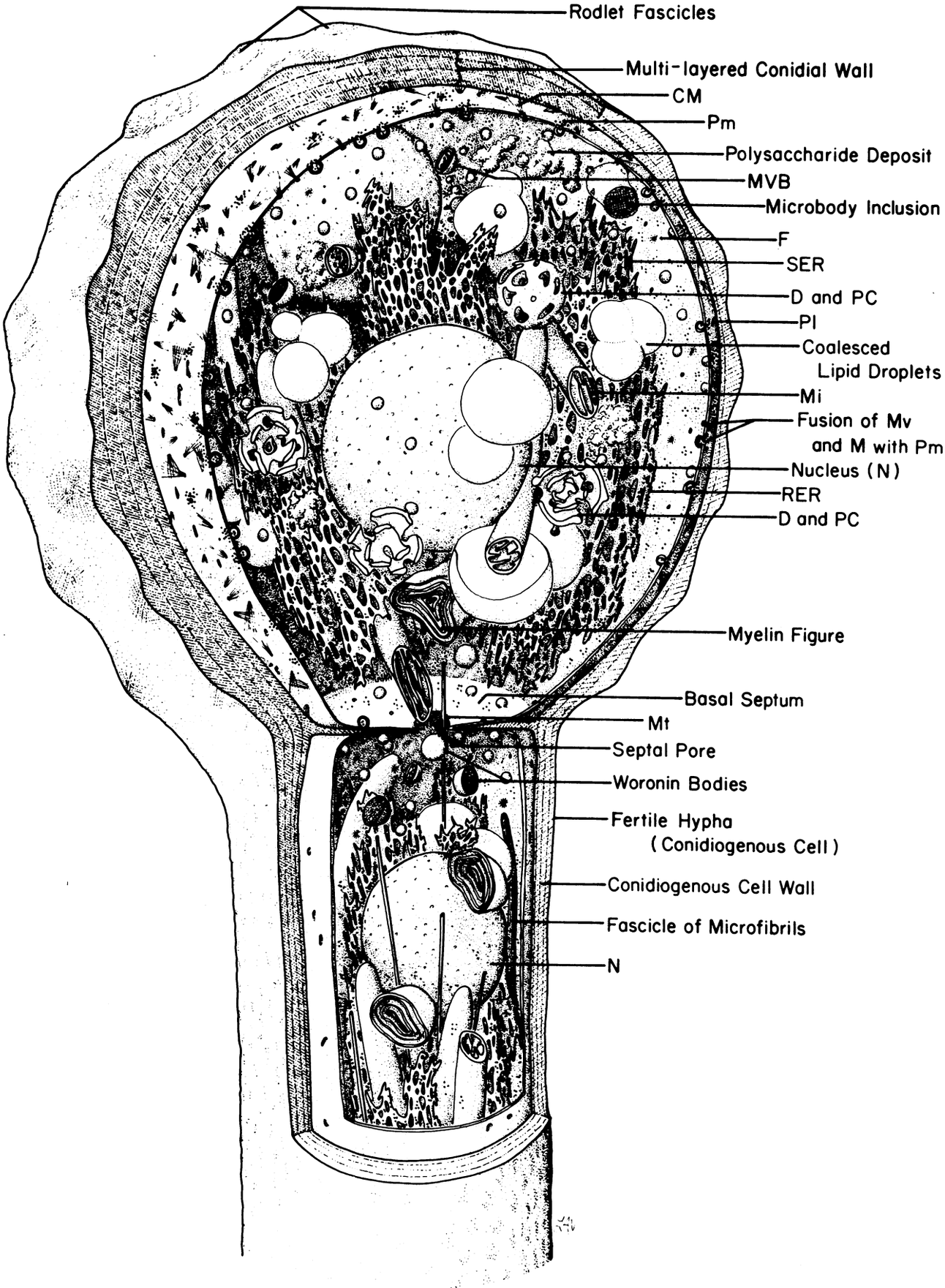


FIG. 3. Diagrammatic interpretation of cytological aspects of a blastic conidium. See Fig. 2 for abbreviations.

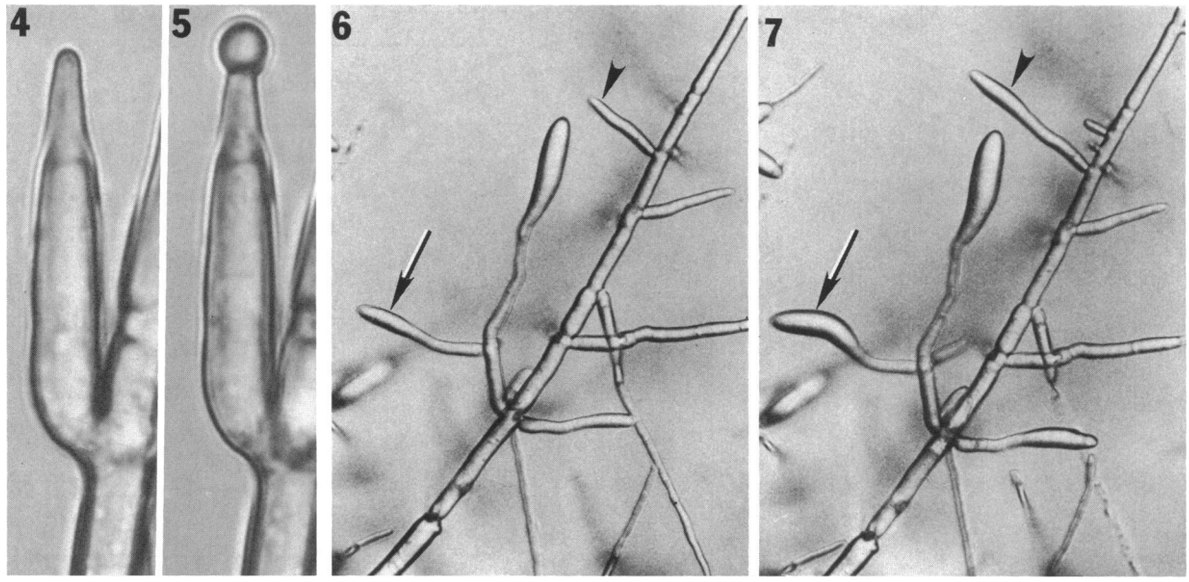


FIG. 4 and 5. Time-lapse photomicrographs of *Cladobotryum varium* showing the initiation of a blastic conidium at the fertile apex of the conidiogenous cell. Elapsed time = 30 min. ×2,090.

FIG. 6 and 7. Time-lapse photomicrographs of *Microsporum gypseum* showing initiation of holothallic conidia from fertile hyphal branches (corresponding arrows and arrowheads). Elapsed time = 30 min. ×550.

pointed out, the region of the fertile hypha which gives rise to one or more blastic conidia is typically delimited from its supporting mycelium by a perforate septum (Fig. 1B), which may still permit organelle movement between adjacent compartments (95). This fertile hyphal segment (conidiogenous cell) may cease further development (Fig. 1H), or give rise to a succession of blastic conidia (e.g., Fig. 1L, M, and P). Thin sections of blastic conidium initials have revealed that the Spitzenkörper has disappeared and numerous mitochondria, lipid bodies, dictyosomes with proliferating cisternae, and extensive endoplasmic reticulum are contained within the swollen extension of the fertile hypha (95, 96, 181, 316, 406, 410, 414). The presence of cytoplasmic microtubules at the isthmus between the conidium initial and conidiogenous cells (60, 64, 72, 82, 178, 182) suggests that migration of the above organelles has been directed into the tip from subapical regions (Fig. 3). Based on the available evidence discussed above for the association between ionic currents and directional movement of organelles during hyphal tip growth, it is possible that alteration of an ion gradient comparable to that resulting from ionophore application may arrest polarized growth and initiate events of blastic development. These cytoplasmic alterations may be accompanied by equally significant changes in cell wall growth and differentiation at the fertile hyphal apex. As pointed out earlier, wall plasticity is maintained at the growing hyphal tip but is reduced over a short gradient toward the distal regions of the extension zone (363), apparently due to glycan chains that interlace with chitin microfibrils forming aggregates of increasing dimensions and complexity (322, 371). If extension growth of the vegetative hypha is abruptly stopped, for instance, by osmotic shock, the entire extension zone becomes rigidified in about 40 s (347). If regrowth of such osmotically shocked hyphae is allowed to resume before the extension zone becomes complete rigidified, new growth occurs from the residual elastic wall at the extreme tip. The arrest of polarized (hyphal) growth and initiation of isotropic growth (blastic conidium formation) may involve subapical wall rigidification but maintenance of wall plasticity at the apical dome (Fig. 4 and 5). A distinct separation of rigidified and plasticized wall zones may be a critical factor in converting the tapered, conical tip of the hypha into a spheroidal conidium.

Even at the early stage of conidium ontogeny illustrated in Fig. 5, a newly formed, thin inner wall layer encompasses the "blown-out" apex (95, 96). Intussusception of new wall material in the conidium initial, like the hyphal tip, involves transport of wall precursors within cytoplasmic vesicles and delivery of these products to the zone of wall differentiation upon fusion of vesicles and plasmalemma. The structures labeled dictyosomes (D) in Fig. 2 and 3 have been found within the sporangia of certain sporangiospore-producing fungi, including *Gilbertella persicaria* and *Mucor mucedo* (42, 181), as well as fertile hyphae (conidiogenous cells) and conidium initials of imperfect fungi (78, 96). Bracker (42) first suggested that these structures represent functional equivalents of Golgi bodies. In cross section they appear as rings of cisternae with vesicles apparently blebbing from their outer circumference. The accumulation of these organelles and multivesicular bodies within the swollen apex of the conidiogenous cell (Fig. 3) may provide for the increased population of macro- and microvesicles (chitosomes?) necessary to shift from a restricted area of chitin synthetase and wall lytic enzyme activity, to the rapidly expanding surface area involved in wall biosynthesis, intussusception, and modification during blastic development. The conidiogenous cell at this early stage of conidium formation contains one or more nuclei which may be in the process of dividing, while the conidium initial is typically devoid of nuclei (82, 349). At the time of initiation of the basal septum which delimits the conidium from conidiogeneous cell, one to several nuclei are present in the swollen apex. Extranuclear microtubules, microfilaments, and microfibrils most likely play important roles in nuclear migration into the conidium initial, even

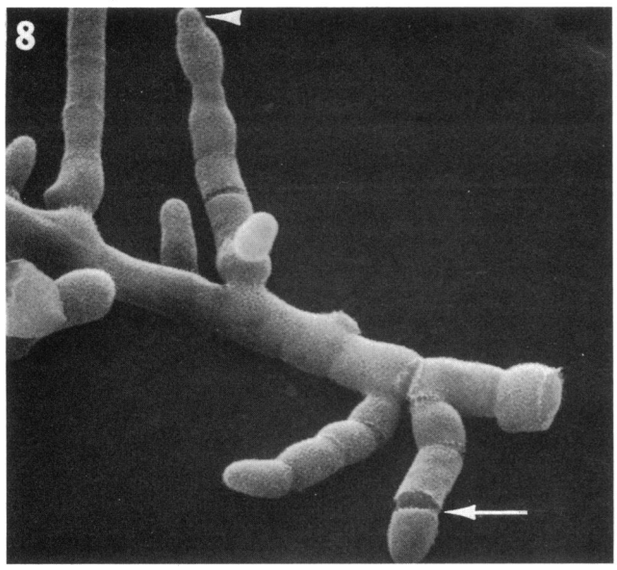
after intercellular movement of organelles is restricted to the narrow septal pore (Fig. 3) (39, 71, 72, 227, 334–346).

The developing propagule accumulates numerous additional organelles and cytoplasmic deposits which are characteristic of the conidial fungi (Fig. 3). Concentric arrangements of membrane (373), referred to as myelin figures (82), have been demonstrated in both chemically fixed and cryofixed cells. These are considered to be deposits of excess cell membrane lipid, possibly serving as a storage reserve within conidia and conidiogenous cells (60, 195). Lipid deposits commonly occur in conidia as coalesced droplets (Fig. 3) surrounded by "half-unit" membranes (166, 204). Both lipid and polysaccharide deposits (82) probably serve as energy reserves for the conidium once it has separated from its parent hypha. The freeze-etch technique (306) has revealed abundant folds, or invaginations of the plasmalemma (76), which are also thought to be excess membrane that accumulates as the conidium undergoes maturation. Plasmalemma invaginations are most numerous in dormant conidia and stationary-phase yeast cells (404). During conidial germination, the portion of the plasmalemma that surrounds the germ tube is smooth except for faint "scars" which represent previously invaginated regions (203). A similar absence of invaginations was noted in freeze-fractures of young buds of yeast cells (404). These observations suggest that the plasmalemma is capable of accumulating excess membrane in preparation for an abrupt outgrowth of the cell before synthesis and incorporation of new plasma membrane becomes synchronized with cell growth (76). Discrete vesicles are also observed between the plasmalemma and newly formed wall of the developing conidium. Serial sections have distinguished these paramural organelles, termed lomasomes (309), from multiple, localized infoldings of the plasmalemma which are referred to as plasmalemmasomes (200). Lomasomes have been suggested to contribute to the synthesis of new wall material (182, 200, 278, 435, 451), particularly during secondary thickening of the wall of thallic conidia discussed below (95, 96). The details of how lomasomal vesicles participate in wall biosynthesis are still unknown. Microbodies are unit-membrane-bound organelles with various demonstrated metabolic functions, such as catalase and H_2O_2-producing oxidase activities (204, 293, 464). The identification of these organelles is, therefore, dependent on electron microscopy and cytochemical localization of enzyme activity (330). Fungal microbodies often contain paracrystalline or crystalline inclusions (Fig. 3), which provides a morphological feature for easy identification (293). Woronin bodies, which may be developmentally and functionally related to microbodies, are commonly observed close to septa and considered to act as "safety valves" since they readily become lodged in septal pores when cells separate or an abrupt change in turgor pressure occurs (95, 103, 338). Ultrastructural evidence indicates that Woronin bodies originate from homogeneous, electron-opaque, and sometimes paracrystalline inclusions of microbodies which move into evaginations of the latter and are pinched off by constriction and fusion of the encompassing membrane (58, 95, 293, 438).

Thallic Development

Time-lapse photomicrographs of holothallic conidium formation in *Microsporum gypseum* are presented in Fig. 6 and 7. Several features of thallic development are illustrated by this species (78, 95, 96, 143, 144). Conidium differentiation is initiated after cessation of polarized growth of the fertile hypha. Rather than an expansion of the tip, which is characteristic of blastic development (cf. Fig. 4 and 5), the thallic conidium of *M. gypseum* develops by the gradual swelling of a large, terminal, preexisting segment of the fertile hypha (arrows and arrowheads in Fig. 6 and 7). This swelling process continues for approximately 1 h (95) and is associated with a uniform thickening of the wall of the conidium initial (143). Conidiogenesis apparently involves some intussusception of wall microfibrils, which should be referred to as "secondary intussusception" (226), since subapical extension growth does occur during this type of thallic development (cf. Fig. 4 and 5). Simple apposition of wall material probably also occurs as the conidium wall thickens and becomes multilayered (95, 352). As previously mentioned, ultrastructural studies have demonstrated that abundant lomasomes lie adjacent to the plasmalemma of the young thallic conidium and have been suggested to participate in secondary wall differentiation (95). Appropriate labeling experiments are still required to explore this proposal. Early in holothallic development (Fig. 1C and D), a septum delimits the fertile segment from the supporting hypha. The septum still permits cytoplasmic continuity between adjacent cells (78). Initiation of this septum in *M. gypseum* appears to be synchronized with the arrest of tip growth, and it is tempting to speculate that these are integrated events. Dermatophytic fungi, including species of *Trichophyton*, *Epidermophyton*, and *Microsporum*, demonstrate comparable mechanisms of conidium formation (96). These medically important fungi represent excellent models, albeit little explored, for investigations of ultrastructural and biochemical aspects of the thallic mode of conidiogenesis.

Thallic development may also involve intercalary differentiation of a preexisting, hyphal segment into a single, holothallic conidium (96, 128). The descriptive term holothallic refers to the incorporation of all wall layers of the fertile hypha into that of the conidium (95). The term chlamydospore, which has been used indiscriminantly in mycological literature for identification of a multiplicity of different cell types (169, 247), has classically been applied to "a thick-walled, non-deciduous, intercalary or terminal asexual spore made by rounding up of a cell or cells" (3). This developmental concept is essentially the same as that derived for holothallic conidia (428). Both cell types are capable of germination under suitable conditions, a feature which would exclude the large, sterile, aberrant cells of *Candida albicans* ("chlamydospores"; 250, 309) from this ontogenetic category (294). No secession mechanism has evolved for chlamydospores, while most terminal, holothallic conidia secede from the parent hypha by dissolution of their basal cell (i.e., rhexolytic secession; Fig. 1D). The chlamydospore wall is more resistant to selected enzymatic degradation than many conidial walls (168, 169, 331, 368, 389, 416, 417). This characteristic probably contributes to the exceptional ability of chlamydospores to survive under unfavorable conditions and has been partly ascribed to the deposition of an outermost, pigmented, and apparently impervious wall layer (7). Chlamydospores are particularly rich in lipid reserves (337, 408), which also contributes to their survival capacity. The cells are stimulated to form under certain hypertonic growth conditions (388), when appropriate concentrations of conidial cells are transferred from high-carbon-containing media to distilled water (366, 367), or under low oxygen tension and temperature stress (17). In spite of their apparent developmental similarities to thallic



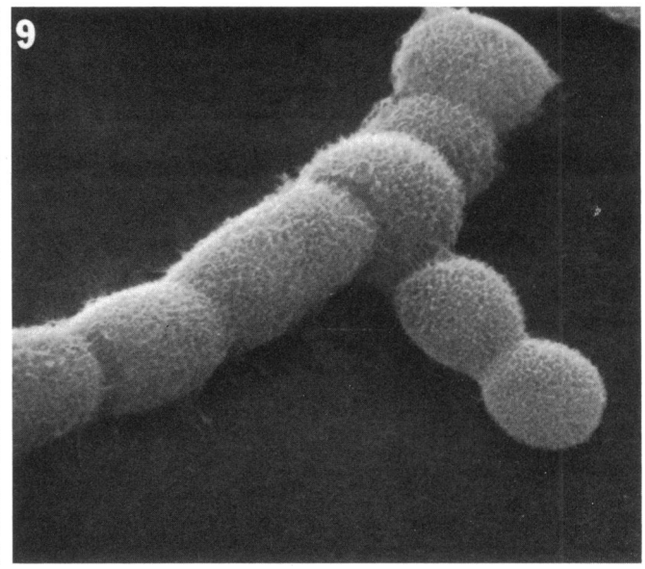


FIG. 8. and 9. Blastoarthric development in *Trichosporon beigelii*. Arrow in Fig. 8 indicates disarticulation of conidial (thallic-arthric) chain, while arrowhead locates blastic conidium initial. Figure 9 shows initiation of an acropetal chain of conidia from a swollen, thallic-arthric conidium. ×2,000 and 5,200, respectively.

conidia, chlamydospores represent a structurally and physiologically distinct cell type (69, 70, 169, 255).

Two modes of thallic-arthric development are largely distinguished on the basis of whether the hyphal wall remains as part of the conidial wall (holoarthric conidium formation; Fig. 1F and E), or whether the hyphal wall eventually separates from the newly differentiated wall of the endogenously formed conidium (enteroarthric conidium formation; Fig. 1F and G). The former is exemplified by *Geotrichum candidum* (76, 88), while the latter mechanism of conidiogenesis is illustrated by *Sporendonema purpurascens* (76) and *C. immitis* (100). Arthroconidium formation in *Trichophyton mentagrophytes* was originally interpreted as holoarthric (36, 195), but on the basis of recent ultrastructural studies (191) is now considered to be enteroarthric. Alternation between holoarthric and enteroarthric modes of conidium formation have been reportd in *G. candidum* and *G. loubieri* (358, 359). The original hyphal wall may or may not remain intact during conidial maturation. The significance of this seemingly incidental feature of wall differentiation is discussed later in reference to the structure, chemistry, and immunoreactivity of wall components in *C. immitis*. Typical thallic-arthric conidia arise from fertile hyphae which are morphologically similar to vegetative hyphae, except that tip growth has been arrested, secondary wall thickening and multiple septation along the length of the fertile segment have been initiated, and eventual disarticulation of the chain occurs by schizolysis or rhexolysis, resulting in the passive dispersal of the propagules (76, 88).

Blastoarthric Development

Branched chains of holoarthric conidia of *Trichosporon beigelii* are shown in Fig. 8. The partial disarticulation of one chain of cells is evident (arrow). Another fertile hyphal branch reveals stages of both blastic development (arrowhead) and thallic-arthric conidium formation. Acropetal chains of blastic conidia may arise directly from swollen, holoarthric conidia in this pleomorphic fungus (Fig. 9). Turian (410, 411) has demonstrated that macroconidiation in the *Monilia* state of *Neurospora sitophila* can be manipulated under experimental growth conditions so that both blastic and thallic modes of conidium ontogeny occur along aerial chains arising from the same mycelium. Blastoarthric development is particularly common among the pigmented, conidial yeasts (96), also referred to as the "black yeasts" (118), which attests to the morphogenetic plasticity of this group of microorganisms.

SEPTATION AND SECESSION

Septum Initiation

The events regulating septum formation have been critically examined in yeast cells, particularly temperature-sensitive (*cdc*) mutants of *Saccharomyces cerevisiae* (55–57, 185–187, 375) and *Schizosaccharomyces pombe* (299, 393). Septation is the final and essential event of the budding process which culminates in secession of daughter cell from maternal cell. One would expect, therefore, that the timing of septation would be synchronized with events which partition cytoplasmic components between these two cells. Indeed, mutants arrested in deoxyribonucleic acid synthesis and nuclear division, fail to construct a septum (188). An additional mutant has been identified in which bud formation occurs but cytokinesis is blocked. The dividing cells were unable to form a normal septum (186). Septation has also been examined in yeast protoplasts which had begun regeneration of their cell wall (142). Septum formation occurred in the absence of a fully differentiated outer wall, which the author suggested is an indication that the signal initiating septation is not associated with the original cell wall but some other cell structure. On the other hand, the outer wall is a necessary prerequisite for subsequent development (anchoring) of the septum. A relationship between septation and karyokinesis is well established in yeasts. For example, the time between karyokenesis and onset of septation in *Schizosaccharomyces japonicus* var. *versatilis* is fairly constant (33 ± 10 min) (142). The signal which initiates septation is probably issued during karyokinesis (154, 299). In wild-type strains, the nucleus begins to migrate into the bud some

time after deoxyribonucleic acid replication (194). During early nuclear division, the spindle microtubules are not oriented parallel to the long axis of the proliferating cell (52, 351). Initial migration of the nucleus into the daughter cell is probably not influenced by the spindle but rather by extranuclear microtubules (91). Prior to completion of telophase, however, the spindle becomes oriented parallel to the long axis of the cell (304, 351) and is then an influential factor on nuclear migration.

In contrast to the extensive body of literature on cytokinesis in yeasts, much less is known of the events which regulate initiation of septum formation in hyphae (154) and conidia (both blastic and thallic) (76, 95). An early indication of septum formation is a circumferential invagination of the plasmalemma, a process which may be mediated by a juxtaposed ring or belt of microfilaments. The presence of a microfilamentous ring at the site of septum initiation was first recognized in *S. cerevisiae* (53) and has subsequently been reported in hyphae (154, 212). Freeze-substitution preparations have demonstrated that the microfilaments lie closely appressed to the invaginated plasmalemma and extend inward toward the center of the cell (212). Girbardt (154) determined that the "microfilamentous septal belt" appeared in hyphae of *Trametes versicolor* 2 to 3 min before the first signs of centripetal growth of the septum. It is still not known whether these microfilaments are capable of contractility, which could contribute to the membrane invagination process. Girbardt (154) has offered another plausible explanation for their presence: the microfilamentous belt may serve as a mechanical device for entrapment of secretory vesicles involved in septal wall biosynthesis, as well as interception of other organelles which "partially fulfill the demand for sequestration of factors needed for septum formation." Intussusception of wall material appears to involve fusion of microvesicles (chitosomes?) with the invaginated plasmalemma (212) and results in development of a gradually thickening disk (Fig. 3) which is composed primarily of chitin microfibrils (227). It is possible that, once centripetal growth of the disk is initiated, further incorporation of wall material into the developing septum pushes the plasmalemma and microfilamentous belt inward, rather than the latter functioning as a contractile element during early septum formation (154). The time required for completion of the process of septation in hyphae of *Alternaria solani* (256) and *N. crassa* (227) has been estimated at 2 and 4 min, respectively.

Septal Pores and Plugs

Septal ultrastructure has long been considered a reliable character for distinguishing between ascomycetous and basidiomycetous fungi (307, 308). A typical ascomycete septum is illustrated in Fig. 10. The cross wall tapers toward the center of the cell, and it seems that at a certain stage of centripetal growth the amount of septal wall synthesis is dramatically reduced and then arrested, leaving a central pore approximately 0.05 to 0.5 μm in diameter (173) through which cytoplasmic continuity between adjacent cells can be maintained. The more elaborate pore apparatus of a typical basidiomycete cross wall, referred to as a dolipore septum, is composed of a central barrel-shaped swelling of the wall covered on both sides by a perforated membranous cap (43, 44, 310). Ingrowth of the septum in this case culminates in a marked increase in wall synthesis and differentiation in the region of the central pore. Morphological intergradations between these two basic types of septa are recognized (262, 281, 405), as well as certain artifacts of dolipore septal ultrastructure (213), and the phylogenetic implications of such characters are uncertain (201). Nevertheless, identification of septal morphology has contributed significantly to considerations of whether a particular conidial fungus has an ascomycetous or basidiomycetous affinity (77). Occurrence of mainly simple, uniperforate septa of the type shown in Fig. 10 among the Deuteromycetes supports the contention that most conidial fungi are related to Ascomycetes. A few species demonstrate characteristic basidiomycetous septa (255). In the case of *Sporothrix* spp., the generic concept is currently being reevaluated since the discovery of both ascomycetous and dolipore septa in representative species of this imperfect fungus (381).

Woronin bodies (Fig. 3 and 10), which were originally identified by light microscopy (48) and later described by using the electron microscope (41), are spheroidal, unit-membrane-bound, electron-opaque organelles sometimes having an internal lattice structure in thin section (5, 173, 177, 214, 407). Several Woronin bodies are commonly observed in a single thin section which passes through, or is adjacent to, the septal pore. The organelles are located on both sides of the septum in the vicinity of the pore (Fig. 10) and are apparently not displayed by cytoplasmic streaming (173). Their chemical composition is mainly protein (214, 292, 295), but detailed analysis awaits isolation and characterization of Woronin bodies in vitro (C. E. Bracker, M. J. Powell, and J. Ruiz-Herrera, Proc. 3rd Int. Mycol. Congr., p. 27, 1983). As mentioned previously, ultrastructural evidence suggests that Woronin bodies originate as inclusions of microbodies which are incorporated into vesicles formed by evagination of the latter organelles (58, 438). Woronin bodies have been thought to serve as emergency safety plugs, capable of sealing the septal pores of ascomycete and deuteromycete hyphae and conidia (45, 95, 104, 292, 338), and thus preventing extensive loss of cytoplasm. This hypothesis was recently tested in hyphae of *Penicillium chrysogenum* by examining the ultrastructure of septal pores at specific time intervals after the filaments were severed (103). Woronin bodies had plugged 38.6% of the pores in the damaged region of the colony within 3.6 s and about 94% within 20 s of cutting. The authors determined that not only the septa immediately adjacent to the damaged compartment were sealed, but also those some distance from the ruptured compartment were plugged by Woronin bodies. Because of the arrangement and number of these organelles in the central region of the septum, it is feasible that a Woronin body could passively move into the depression of the septal pore (Fig. 10) as outflow of cytoplasm occurs from the damaged compartment. However, Collinge and Markham (103) have also suggested that a microfilament or microtubule-mediated response of Woronin bodies to hyphal damage could be involved in an active plugging mechanism. Once a Woronin body has become lodged in the pore separating an intact and damaged compartment, growth of the septal wall over the spheroidal plug may ensue (Fig. 11 and 12), thus permanently sealing the cross wall. Similarly, in the case of seceded conidia the Woronin body is usually cemented into the pore of the basal septum with an electron-dense deposit (82, 95).

Mechanisms of Conidial Secession

Ultrastructural investigations have also indicated that gradual occlusion of the perforate septum may occur by

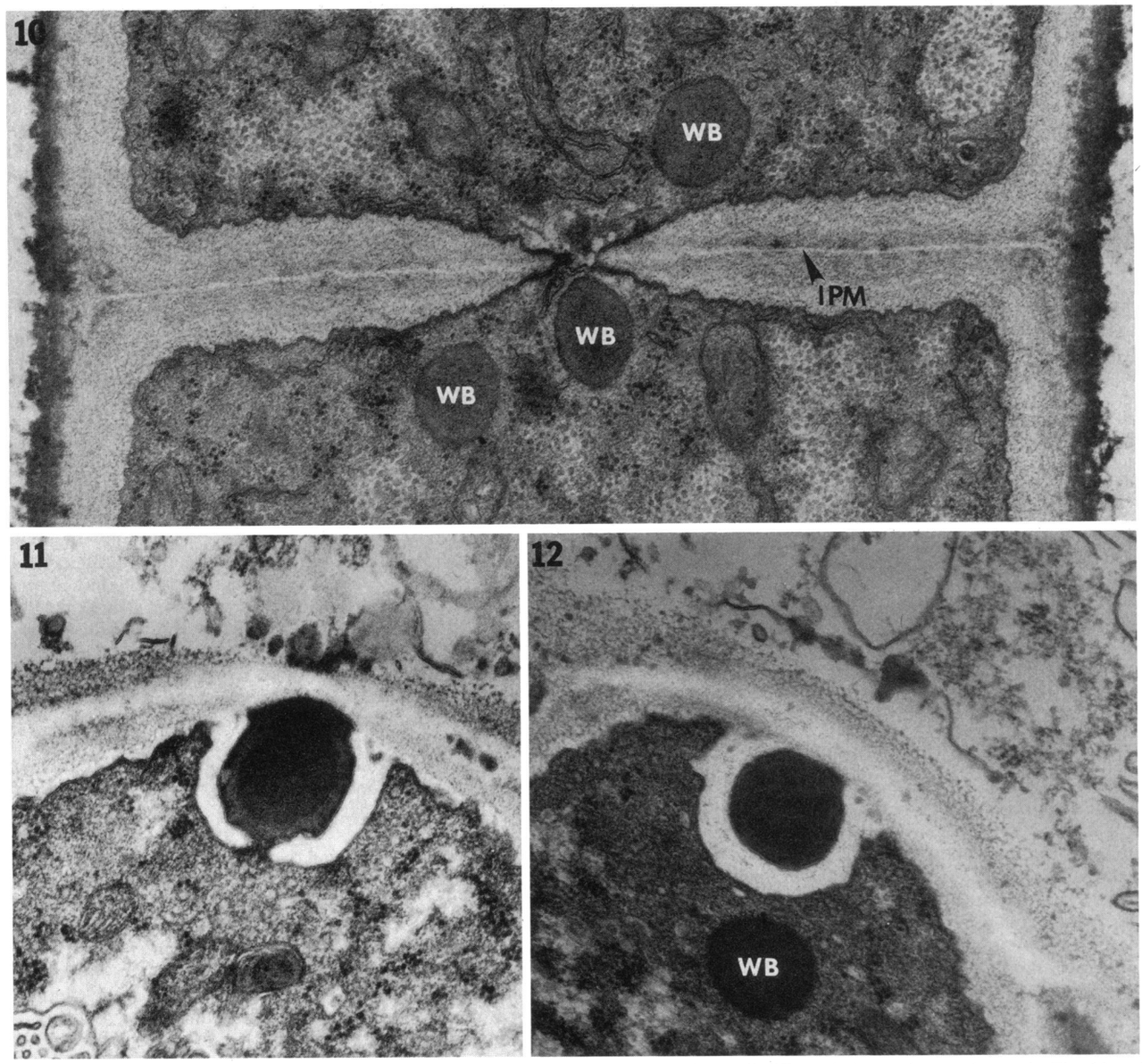


FIG. 10–12. Thin sections of uniperforate septa of *Drechslera sorokiniana* showing wall differentiation and central pore in Fig. 10 and septal pore plugs in Fig. 11 and 12. IPM, Interplate matrix; WB, Woronin bodies. ×46,000, 48,000, and 48,000, respectively.

deposition of electron-dense or fibrous material or both at the perimeter of the pore in the absence of Woronin bodies (95, 227). This plugging mechanism has been identified in senescent cells (62), as well certain types of conidia which develop in chains and have specially differentiated septa. Examples of the latter include the holoarthric conidia of *G. candidum* (76, 319) and phialoconidia of *Aspergillus clavatus* (182). Their septa are illustrated in Fig. 13A and B, respectively. The conidial septa of *G. candidum* are multiperforate with narrow plasmodesmal canals (8.5 to 9.5 μm in diameter) extending through the cross wall between adjacent cells (41, 95, 173, 192, 386). The septa of vegetative hyphae produced by this same fungus are the typical uniperforate type (76) shown in Fig. 10. The mode of multiperforate septum development has not yet been critically investigated, although dissolution of pores or spokelike ingrowth of the cross wall has been suggested (41, 192). Steele and Fraser (386) have presented evidence that plasmodesmata are formed while the septum is developing, and thus partially developed septa have plasmodesmal canals. The latter may permit translocation of ribosomes, endoplasmic reticulum, and certain cytoplasmic deposits between cells, but not nuclei, mitochondria, and other large organelles. Once the cross wall has formed, each compartment of the fertile hypha of *G. candidium* (Fig. 1E) contains at least one nucleus. Further discussion of the karyological events during conidiogenesis in this fungus is presented below. Just prior to disarticulation of the conidial chain, the plasmodesmal canals become occluded with an electron-opaque deposit (95). The cross walls of juxtaposed cells are

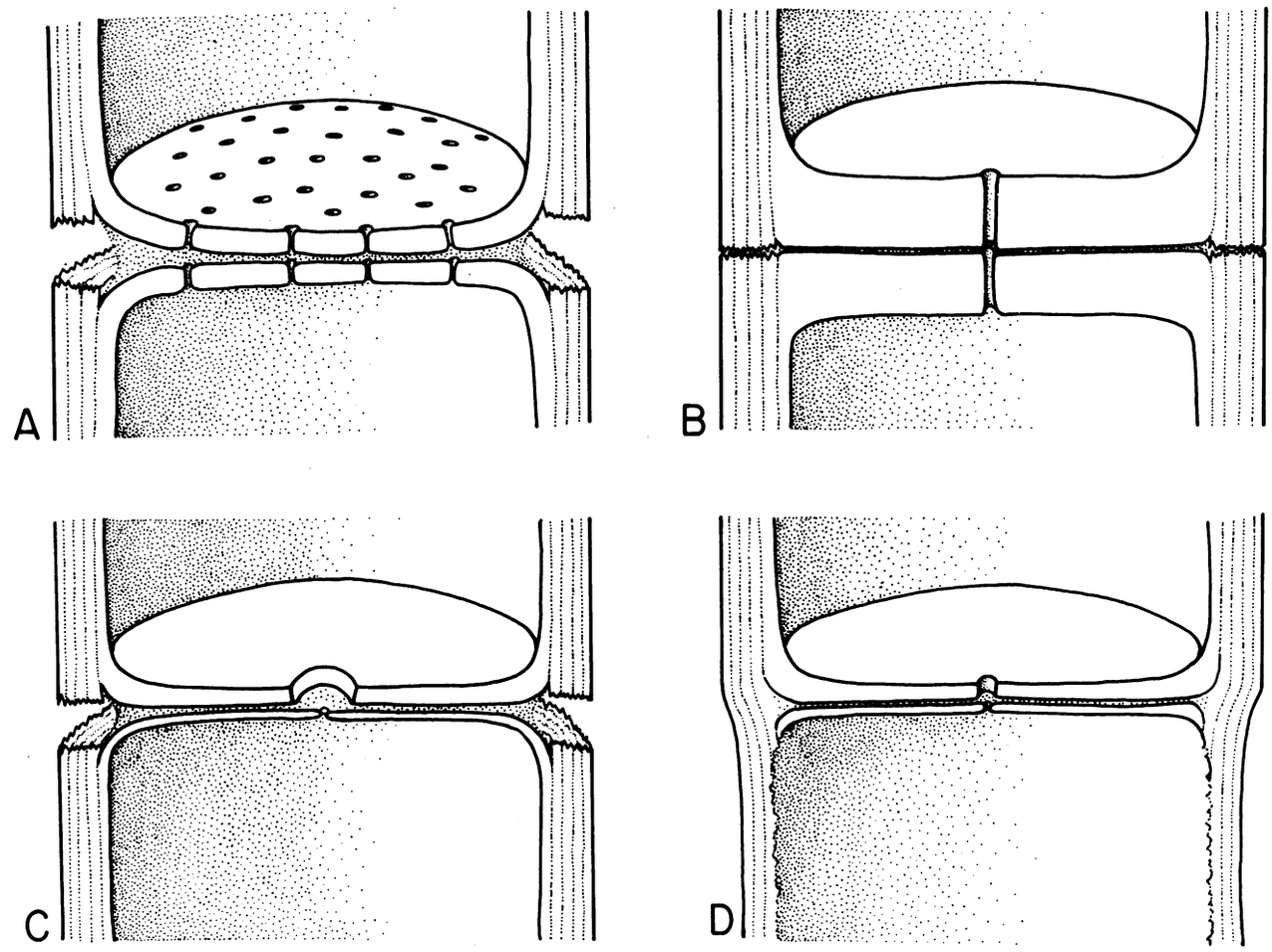


FIG. 13. Examples of septal wall structure and mechanisms of conidial secession. A, *G. candidum*; B, *Aspergillus clavatus*; C, *Scopulariopsis brevicaulis*; D, *C. immitis*.

of equal thickness, and the simultaneous swelling of each conidium of the chain leads to mechanical separation of the two apposing septal wall layers (Fig. 13A) (76, 88). Ultrastructural examination of early septal development reveals that the cross wall is composed of two fibrous, electron-translucent layers separated by a thin, electron-transparent zone (cf. Fig. 10), which Gooday and Gow (161) have called the "interplate matrix." This is a common morphological feature of septal wall differentiation in ascomycetes and deuteromycetes (51, 78, 162, 227). In the case of certain conidial septa, appearance of a distinct electron-transparent zone is indicative of localized wall lysis which is part of the secession process (82). This aspect of conidial separation was referred to in the earlier discussion of ontogeny and classification as schizolysis. The thin, intermediate, transparent zone becomes more prominent as conidia mature, which is considered to be the result of concentrated wall lytic activity (96). The participating enzymes may have been originally transported across the plasmalemma (macrovesicle fusion?) on both sides of the developing septum to fulfill a role in septal wall formation (i.e., balance between wall synthesis and lysis). As the basal septum of the conidium matures, it is suggested that concentrated lytic enzyme activity leads to the separation of two distinct septal wall layers which are then subjected to mechanical stress as the apposing cells swell. The cross walls of *G. candidum* become convex, the continuous outer (lateral) wall layer(s) eventually ruptures (Fig. 13A), and the conidial chain disarticulates (95).

In *A. clavatus*, young conidia near the conidiogenous cell apex do not readily secede from the adjacent conidium in the chain. Ultrastructural examinations of their basal septa have revealed a very different morphology (Fig. 13B) to that of *G. candidum* (95, 182). A narrow plasmodesmal canal is visible which becomes occluded soon after the conidium has differentiated at the fertile cell apex. The two apposing cross walls are particularly thick and distinguished by only a thin, electron-translucent zone (Fig. 13B). The outer (lateral) wall layer between adjacent conidia remains intact. Older conidia in the chain, more distant from the apex of the conidiogenous cell apex, secede as a result of mechanical stress. The transverse fracture plane follows through the thin electron-transparent zone between the two thick septal wall layers and through the adjacent lateral wall (Fig. 13B). Most conidia of *Aspergillus* and *Penicillium* spp., which demonstrate similar secession mechanisms, become very dry at maturity (325). Low moisture content, especially in the cell walls, increases susceptibility of the conidial chain to mechanical fractures due to air movement, impact of rain droplets, insect foraging, etc. The basal septum of

phialoconidia produced by *Sphaerostilbe ochracea* lacks a distinct, central pore as well as Woronin bodies (155). In contrast to *Aspergillus* spp., the septum is thin walled and conidia accumulate in droplets at the phialide apex. It appears that the absence of both Woronin bodies and a well-differentiated pore in the basal septum of the conidium are characteristic of phialoconidiogenesis (59, 64, 155).

A third mechanism of conidial secession is demonstrated by those forms which give rise to a succession of blastic conidia from a percurrently proliferating conidiogenous cell apex. In this case, the outer conidial wall layer separates from the growing wall of the fertile apex as each new conidium is formed. This developmental process is exemplified by certain phialide-producing (Fig. 1L) and annellide-producing (Fig. 1M) species, such as *Metarrhizium anisopliae* (175) and *Scopulariopsis brevicaulis* (82, 174), respectively. The distinguishing features of wall differentiation during conidial secession are illustrated in Fig. 13C. The upper layer of the cross wall forms the thick, basal septum of the conidium. Its prominent, central pore is permanently sealed prior to conidial release. The thin, lower septal wall layer delimits the new apex of the proliferating conidiogenous cell, which demonstrates variable amounts of extension growth (i.e., polarized tip growth) before it differentiates into a new blastic conidium. Ingrowth of the lower septal wall layer continues until only a narrow, central channel remains (95, 175). The latter is sealed at the onset of percurrent proliferation. Initial separation of the two septal wall layers occurs along a lytic zone (schizolysis) which, in the case of annellidic development, determines the point where the rigid, outer, lateral wall layer will fracture when extension growth of the fertile apex pushes the conidium upward (Fig. 13C) (82, 95).

The final mechanism of conidial secession (Fig. 13D) was referred to earlier in this review as rhexolysis because it involves a fracture through a cell adjacent to the conidium, rather than between septal wall layers. Release of holothallic conidia of *M. gypseum* (Fig. 1D) (82, 95), enteroarthric conidia of *C. immitis* (Fig. 1G) (100, 396, 398), and blastic conidia of *Gonatobotryum apiculatum* (Fig. 1I) (73) exemplify rhexolytic secession. The septum between cells of the fertile hypha of *C. immitis* is perforated by a tiny, central pore which is occluded early in conidial development. As described in previous examples, the septal wall differentiates into two layers separated by an electron-transparent (lytic) zone. However, during initiation of enteroarthric development it is evident that the two layers of the septum and lateral walls of adjacent cells do not thicken equally. Wall synthesis in one cell is arrested and its contents eventually autolyze, while the wall encompassing the adjacent cell continues to thicken and becomes the inner conidial wall (76, 96). The lateral wall of the autolytic cell becomes thin and fragile and eventually fractures, resulting in disarticulation of the conidial chain (Fig. 13D). In *Gonatobotryum apiculatum*, which gives rise to chains of blastic conidia from fertile ampullae (Fig. 1O), a small, intermediate cell is delimited between each pair of propagules (Fig. 1I). In contrast to *C. immitis*, the cross walls reveal prominent septal pores which permit cytoplasmic continuity between the ampulla and apically budding cell of the chain (i.e., acropetal chain of conidia; 95). The wall of the intermediate cell remains intact as long as cytoplasmic continuity is maintained. Once the septal pores are sealed, the intermediate cells begin to autolyze, their lateral wall becomes fragile and eventually fractures, and disarticulation of the conidial chain is accomplished.

Septation and Conidiogenous Cell Development

The suggestion that spatial and temporal regulation of septation may occur during cell differentiation in conidial fungi is well illustrated by phialidic (Fig. 1L), annellidic (Fig. 1M), and retrogressive conidiogenous (Fig. 1P) cell development. The phialide gives rise to a basipetal succession of blastic conidia through a rupture in its outer wall layer. The rupture occurs either during formation of the primary phialoconidium or at initiation of the second conidium, and the remaining sleeve of wall material at the fertile apex is called a "collarette" (95). The size of the collarette varies depending on the level at which the circumscissile rupture of the outer wall occurs (cf. Fig. 14A and B). Time-lapse photomicrography of phialidic development in *Phialophora* spp. (81, 86; G. T. Cole and W. B. Kendrick, 11th Int. Bot. Congr., p. 34, 1969) has revealed that secondary conidia emerge through the collarette in "popgun" fashion and accumulate in droplets at the conidiogenous cell apex. The phialide does not appear to elongate during formation of multiple conidia from a single, fertile apex. However, conidiogenesis may be interrupted and the phialide may subsequently undergo polarized extension growth from the same apex (i.e., percurrent proliferation; Fig. 1N) or sympodial proliferation from below the fertile apex (Fig. 1J), followed by resumption of conidium formation from a new locus (86). Thin sections through the collarette of *Trichoderma saturnisporum* (177) have indicated that some elongation of the phialide apex does take place during formation of successive conidia. Such extension growth occurs within the collarette and is, therefore, not visible to the light microscopist (Fig. 14A). Each conidium secedes as a result of shizolysis of the two wall layers of the basal septum in addition to concomitant intussusception of new wall components into the lower layer which leads to elongation of the phialide apex (see Fig. 13C). The outer conidial wall layer ruptures, leaving a ring of wall material inside the collarette (Fig. 14A). The inner conidial wall is continuous with the basal septum and, therefore, homologous with the wall which encompasses the new proliferating phialide apex and subsequently surrounds the next phialoconidium. Septal differentiation is pivotal in maintaining an ordered sequence of ontogenetic events: delimitation and secession of the propagule and initiation of the proliferative phase, which culminates in differentiation of the next blastic conidium.

An alternate sequence of events during phialidic development is illustrated by species of *Penicillium* and *Aspergillus* (95). Instead of the basal septum of each conidium separating into two distinct wall layers, it continues to thicken after delimiting the phialoconidium. The conidia remain in a chain at the phialide apex, held together by the intact septa ("connectives") and continuous, outer wall layer (Fig. 14B; see Fig. 13B). The inner phialide wall undergoes a period of extension growth, presumably by secondary intussusception, which is followed by blastic conidium formation and basal septum differentiation (86). This sequence is repeated many times, resulting in formation of long conidial chains which eventually disarticulate, usually as a result of mechanical disruption (148, 301).

Annellidic development is characterized by a series of ontogenetic events which are essentially the same as those of the type of phialide formation illustrated in Fig. 14A (300). Phialidic and annellidic modes of development were originally defined on the basis of light-microscopic examinations (86, 87, 223) and distinguished by the presence of either a collarette or numerous ringlike scars (annellations) visible at

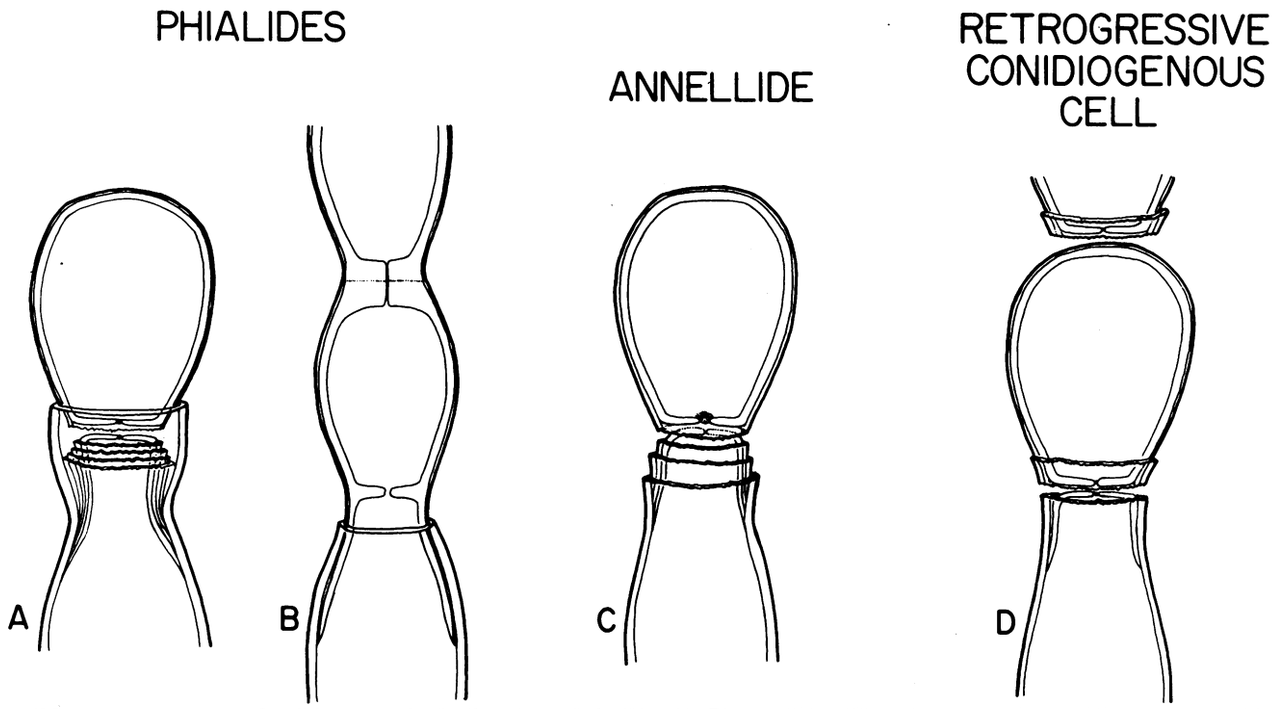


FIG. 14. Arrangement of wall layers at the fertile apices of phialides (A, B), annellides (C), and retrogressive conidiogenous cells (D).

the fertile cell apex. The major difference in these two developmental processes, therefore, is simply the degree of percurrent proliferation which occurs between successive stages of blastic conidium differentiation. In the case of the annellide (176, 178), conidial secession scars are exposed, and in some species they are widely separated (e.g., *Annellophora africana* [223]; *Acrogenospora sphaerocephala* [131]), while in the phialide they are absent (Fig. 14B) or contained within the collarette (Fig. 14A).

Retrogressive conidiogenous cell development, represented by *Basipetospora rubra* (85), *Trichothecium roseum* (252), and *Cladobotryum varium* (89), is characterized by successive shortening of the fertile cell as each blastic conidium differentiates and secedes from the fertile cell apex (Fig. 14D). A ring of outer wall material of the conidiogenous cell adheres to the base of the conidium during septum formation. Extension growth of the lower septal wall layer (Fig. 14D) results in a fracture through the outer fertile cell wall and loss of a segment of its apex.

A striking feature of phialidic, annellidic, and retrogressive conidiogenous cell development is the remarkable degree of regularity in their sequence of ontogenetic events. In each case, polarized tip growth of the conidiogenous cell apex is arrested, followed by primary blastic conidium formation. The conidiogenous cell apex, encompassed by the lower septal wall layer, resumes polarized extension growth over a brief or extended period (Fig. 14A, C and D), or the fertile cell elongates below the basal septum as a result of secondary intussusception (Fig. 14B). Proliferation is followed by secondary conidium development and septum formation. The sequence is repeated at the new apex of the fertile cell which, as a result of distinct ontogenetic events, elongates after formation of each conidium, remains fixed in length, or shortens.

KARYOLOGY AND CONIDIOGENESIS

Patterns of nuclear behavior during conidiogenesis have been examined in a relatively small number of species (76, 95, 179, 180, 250, 349, 458). Nevertheless, at least four distinct nuclear cycles are recognized which are illustrated in Fig. 15. In the first, exemplified by *Gliomastix murorum* (Fig. 15A to E) (180), mitosis occurs at the base of the conidiogenous cell (phialide) and the developing conidium receives one of the daughter nuclei. The fertile cell and conidium are each uninucleate. Mitosis typically occurs at a considerable distance from the conidium initial and the plane of division is parallel to the long axis of the phialide. In *Gliomastix murorum*, the daughter nucleus migrates 10 to 15 μm from the mitotic site to the fertile apex and enters the young enucleate conidium through the pore of its already partially developed basal septum. The chromatin which comprises the conidium initial remains condensed and the uninucleate condition persists in the mature and seceded conidium. The nucleus which remains in the phialide enlarges, its chromatin decondenses, and following a phase of DNA synthesis, the cycle is repeated (180). This same nuclear cycle has been observed in phialides of *Penicillium* (349, 460) and *Aspergillus* (260) species.

Ultrastructural examinations of mitotic nuclei in septate fungi have demonstrated, with few exceptions, that the nuclear envelope remains intact (153, 264). Thin sections have also revealed electron-dense plaques or globular deposits on the outer surface of the interphase nucleus which have been termed nucleus-associated organelles (198, 199, 267). These are the foci at which spindle microtubules terminate. They may also represent the nucleation sites for growth of intra- and certain extranuclear microtubules (G. G. Borisy, J. B. Peterson, J. S. Hyams, and H. Ris, J. Cell. Biol.

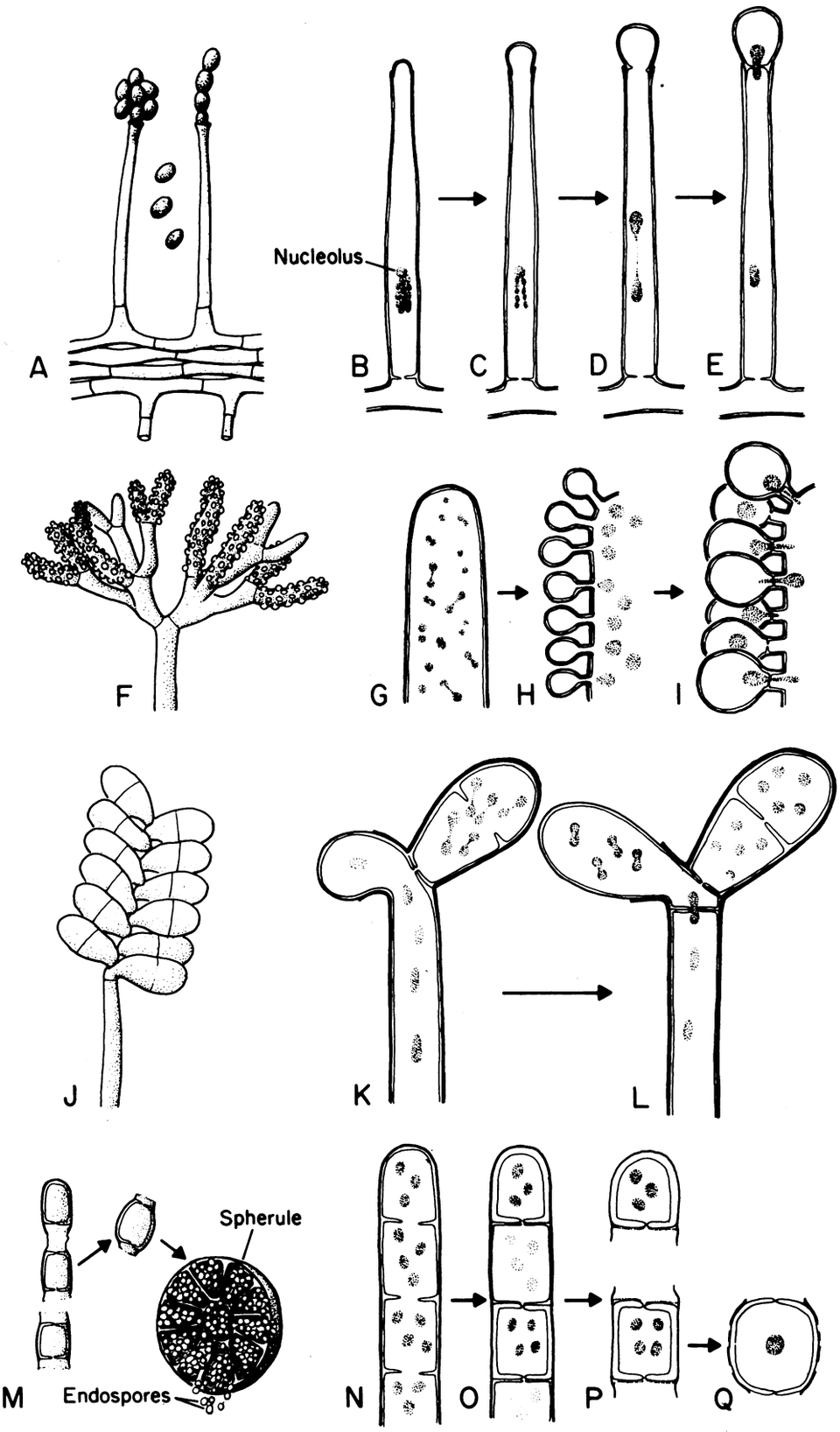


FIG. 15. Examples of nuclear cycles during formation of blastic conidia from phialides (A to E; *Gliomastix* sp.), ampullate conidiogenous cells (F to I; *Chromelosporium* sp.), and retrogressive conidiogenous cells (J to L; *Trichothecium* sp.), and nuclear cycle during enteroarthric conidium formation (M to Q; *C. immitis*).

67:38a, 1975). Under the light microscope, initiation of mitosis in *Gliomastix murorum* is recognized by the appearance of distinct chromatinic granules and usually polar location of the nucleolus (Fig. 15B). The chromatinic granules subsequently become smaller and fewer, and assume a "double track" arrangement (Fig. 15C) (349, 350). The nucleolus may be still visible at this stage of mitosis. The double-track distribution of chromatin is characteristic of mitotic nuclei in the majority of septate fungi examined (264). The spindle occupies the central region of the two barlike masses of chromatin. The next stage of mitosis involves a transverse separation of the double track and subsequent movement of the two chromatin masses toward opposite spindle poles (Fig. 15D). The upper chromatin mass appears to move toward the phialide apex, while the lower one remains more or less stationary (180). A narrow, interconnecting band of chromatin is usually visible between the two masses. During these events of the nuclear cycle, the enucleate conidium initial continues to enlarge and its basal septum begins to form. The daughter nucleus, which had migrated to the phialide apex, appears ameboid as it squeezes through the septal pore (Fig. 15E). The latter is sealed as a new conidium begins to develop and the nuclear cycle is repeated.

The second example of a nuclear cycle associated with conidiogenesis is demonstrated by those forms which first accumulate a large store of nuclei within their fertile cell and then give rise to multiple, synchronously developing, enucleate blastic conidium initials. Each conidium subsequently receives one or more nuclei by migration from the nuclear reservoir in the conidiogenous cell. The karyology of the conidial state of *Peziza ostracoderma* (Fig. 15F to I) exemplifies this cycle (349). Nuclei accumulate in the fertile ampulla as a result of migration from the supporting mycelia as well as nuclear division in situ (Fig. 15G). A large number of nondividing nuclei fill the fertile cell as conidium initials emerge synchronously from its surface. The blastic conidia remain enucleate during their early stages of differentiation but the nuclei within the ampulla become positioned at the base of the denticles (Fig. 15H). A single nucleus migrates through the denticle and pore of the basal septum into each conidium (Fig. 15I). Although nuclei do not enter the initials simultaneously, all conidia become nucleate over a short period of time. The conidial septa are then sealed and the ampullar wall and cytoplasm gradually degenerate, resulting in rhexolytic secession of the propagules (221). Delimited conidia are occasionally binucleate (221), which may be the result of migration of a pair of nuclei from the ampulla into the developing conidium, or mitotic division of the single nucleus after septation is complete.

A variation on this same theme is demonstrated by *Gonatobotryum apiculatum* (250). As above, the ampulla gives rise to synchronously developing, blastic conidia (Fig. 1I), and the events of the nuclear cycle in these two species are very similar. However, each primary conidium of *Gonatobotryum apiculatum* gives rise to a secondary conidium at its apex. This newly formed cell subsequently proliferates, and the developmental sequence is repeated to produce an acropetal chain of popagules (Fig. 10). In contrast to the synchronous development of primary conidia, chains of secondary conidia are formed asynchronously. The single nucleus in the primary conidium divides after secondary conidium initiation, and one of the daughter nuclei then migrates into the newly budded cell while the other remains in the parental cell. This cycle is repeated during formation of each secondary conidium. The sequence of events in this latter process appears to be more highly ordered than that of primary conidium ontogeny (250) and is reminiscent of the karyological events which characterize the yeast cell cycle (91, 187, 383). *Gonatobotryum* spp., in addition to other morphogenetically related genera of conidial fungi (e.g., *Botrytis*, *Botryosporium*, *Oedocephalum*, *Gonatobotrys*, *Nematogonium*), offer unusual models for examining cellular mechanisms which control multiple and synchronous cell development from a single parental cell, as well as sequential steps of bud emergence, bud growth, and cell separation (349).

The third type of nuclear cycle associated with conidial development is demonstrated by such species as *Scopulariopsis brevicaulis* (250), *Scopulariopsis koningii* (174, 179), *Helminthosporium sativum* (220), and *Trichothecium roseum* (Fig. 15J to L) (349). Mitotic divisions in the conidiogenous cell are more or less synchronized. Once the conidium initial begins to form, mitosis in the fertile cell is apparently arrested, and nuclei migrate into the swollen apex (Fig. 15K). Several nuclei are contained by the young conidium after it is delimited by a basal septum. The distinguishing feature of this cycle is that these nuclei then begin to divide synchronously so that the mature propagule contains many more nuclei than the initial (Fig. 15L). In *Trichothecium roseum*, the delimited conidium becomes two celled after a transverse cross wall has formed. The nuclei typically separate into two equal groups during septum development by migrating to opposite poles of the cell.

The final type of nuclear cycle is associated with thallic-arthric development and exemplified by *G. candidum* (76, 250), *C. immitis* (Fig. 15M to Q) (100, 231, 396), *Sporendonema purpurascens* (76, 95), *Coremiella cubispora* (95), and others. Arthroconidia produced by medically important fungi, such as *Trichophyton mentagrophytes* (134, 189, 190, 193) and *C. immitis*, are infectious agents of the pathogen. In spite of the apparent simplicity of this mode of conidiogenesis (76, 88), it represents a potentially useful model of fungal cell differentiation (18, 191). In each case, the fertile hypha undergoes progressive septation, resulting in compartmentalization of one or more nuclei, features which distinguish this cycle from the previous examples. In *G. candidum*, the aseptate, fertile hypha contains fairly regularly spaced nuclei. At first, septation occurs in acropetal succession (88) and most compartments contain two to three nuclei (250). These primary subdivisions of the hypha then randomly undergo further septation, with the cross wall more or less dividing the compartment into equal halves. The newly delimited compartment commonly contains a single nucleus, and most of these cells undergo another mitotic division. Initiation of cross wall formation occurs soon after completion of mitosis and migration of the daughter nuclei to opposite ends of the hyphal segment. In the case of some of the original uninucleate compartments, mitosis occurs but the nuclei remain in relatively close proximity. Further septation does not occur in these compartments (250). Disarticulation of the septate, fertile hyphae yields thallic-arthric conidia which are primarily uninucleate.

The conidia of *Coccidioides immitis* spp. also originate from septate, fertile hyphae, but each of the final subdivisions in this case contain two to five nuclei (Fig. 15N). Those compartments which demonstrate progressive thickening of the encompassing wall layer maintain their nuclear composition, while the cytoplasmic contents of adjacent thin-walled cells undergo degeneration (Fig. 15O). Ultrastructural examination of early stages of autolysis have revealed

hypertrophied mitochondria with atypically arranged cristae and irregular surface ornamentation on nuclear envelopes (76). All nuclei trapped in autolytic cells are soon aborted (Fig. 15O). The seceded conidia, on the other hand, contain their original complement of nuclei (Fig. 15P). Subsequent saprobic development of the enteroarthric conidia of *C. immitis* usually involves hyphal germination and concomitant mitoses which reestablishes the mycelial phase (396). A developmental alternative for this potentially pathogenic fungus is demonstrated when the conidium enters the respiratory tract of a suitable host and swells rather than germinates (Fig. 15M) (100). The round cell undergoes segmentation (i.e., spherule differentiation) and eventually releases a multitude of tiny cells (endospores) which disseminate within the host. All stages of the parasitic cycle of *C. immitis* can be produced in vitro (397), which has permitted laboratory studies of the karyology of this pathogen (232). The swollen arthroconidium (round cell) usually contains a single nucleus, although this uninucleate condition persists for only a short period (Fig. 15Q) (100, 396). The single nucleus of the round cell is distinctly larger than nuclei of the arthroconidia. The uninucleate cell soon becomes binucleate and then undergoes relatively rapid and synchronous nuclear division as it transforms into a spherule. The cytoplasm of the latter becomes segmented into multinucleate units which subsequently differentiate into uninucleate endospores. A still unresolved and pivotal question concerning the karyology of *C. immitis* is whether reduction in nuclear number during differentiation from arthroconidium to round cell is the result of nuclear fusion, abortion, or both (100, 102). The parasitic cycle of *C. immitis* is unique among fungi which produce thallic-arthric conidia. However, the nuclear cycle associated with the saprobic phase (Fig. 15N to P) is essentially the same as that demonstrated by *Sporendonema purpurascens* and *Coremiella cubispora*.

Although the foregoing discussion most likely does not account for all variations in nuclear cycles among the conidial fungi, the examples described represent potentially useful models for studies of interrelationships of karylogical events and conidiogenesis. The application of various chemical inhibitors of specific steps in the nuclear cycle (e.g., inhibitors of deoxyribonucleic acid synthesis and transcription/ribonucleic acid [RNA] synthesis) as well as conidial morphogenesis (e.g., inhibitors of chitin synthesis) may be particularly informative in this regard (320). Further potential of such investigations will be realized when suitable morphogenetic mutants are made available and precise identification of regulatory genes and their expression during the nuclear cycle are possible.

WALL DIFFERENTIATION

Conidial Wall Structure and Chemistry

Thin sections of mature blastic and thallic conidia have generally revealed that the encompassing wall is composed of two or more layers (Fig. 3) (149). The number of wall layers detected is largely dependent on the procedures used for fixation and heavy-metal staining of the specimen in preparation for electron microscopy (285, 368). Freeze-substitution techniques (212), which appear to provide superior preservation of wall ultrastructure, have not yet been used for examination of conidial walls. The particular mode of conidium formation and culture conditions may also contribute to differences in the number of wall layers observed in a single species (286, 287). Typically, a well-defined, electron-translucent layer lies adjacent to the cell membrane, which represents the youngest of the wall components to be synthesized and consists largely of intertwined chitin microfibrils (93, 98, 269). The outer wall layers, on the other hand, vary in texture and electron density. In the case of dematiaceous forms (131, 132), the outer layer(s) appears black in electron micrographs, primarily due to the presence of dark pigment deposits in the wall (129, 130, 339, 446). Such fungal pigments are usually referred to as melanin, even though in many cases evidence for their mode of synthesis and chemical composition are not known. Melanin frequently appears as electron-dense grains, 30 to 150 nm in diameter, within the cell wall (333) and can be readily solubilized in hot 1 M KOH. Extracted melanins demonstrate characteristic infrared spectra (35, 129). Synthesis of these pigments has been attributed to phenoloxidase enzyme systems which have been found in numerous fungi (288, 425). Phenoloxidase systems consist of soluble enzymes with broad substrate specificities, while the alternate pentaketide pathway of melanin synthesis is substrate specific (33, 34). This latter pathway was at first considered peculiar to a few imperfect fungi, such as *Verticillium dahliae* (33, 34, 391, 392, 445), *Pyricularia oryzae* (452), *Thielaviopsis basicola* (443), and *Wangiella dermatitidis* (150), but has recently been suggested to be the predominant mechanism of melanin biosynthesis in the dematiaceous Ascomycetes and Deuteromycetes (442). The physiological roles of melanins in fungi are still not well defined (333). Evidence is available that they function in storage of water and ions (447), confer resistance to lysis by other microorganisms (47, 331), and protect the cell against solar radiation (399). An intriguing possibility is that synthesis of melanin may also be essential for expression of pathogenicity of darkly pigmented fungi which cause disease in both plants (114, 343, 453, 456), and animals (403). Geiss and co-workers (150) have suggested that inhibition of melanin synthesis in *W. dermatitidis*, using agents such as tricyclazole (444), may prevent expression of the zoopathogenic potential of this and other disease-causing, dematiaceous fungi.

The surface of conidia examined by electron microscopy in general appears either smooth or rough and scaly (95). In the latter case, wall components appear to be shedding from the cell surface (82, 181). This phenomenon may be particularly significant from the clinical standpoint for certain allergenic molds (97, 273, 450), in which sloughed wall components interact with tissues of the respiratory tract and could be at least partly responsible for immediate hypersensitivity responses (1). Similarly, the echinulate or tuberculate conidia of certain respiratory allergens and pathogens lose wall components during impact and subsequent interaction with animal tissue which may stimulate a host reaction. These surface ornamentations originate as distortions of the outer conidial wall layer during early growth and subsequently enlarge as localized accumulation of inner wall material results in development of characteristic surface patterns (82, 127, 149). It is axiomatic that the microbial cell wall surface plays a significant role in the colonization of substrates, whether the microorganism is a saprobe or a parasite (361, 377). An appreciation of the importance of cell surface structure and chemistry in bacteria (448, 449) and yeasts (141) is evident, which has led to new insights into the nature of the many types of interactions between these cells and their environment (364, 376). In striking contrast to this impressive volume of literature, there is a paucity of information available on the structure and composition of the conidial envelope (12, 20, 27, 361).

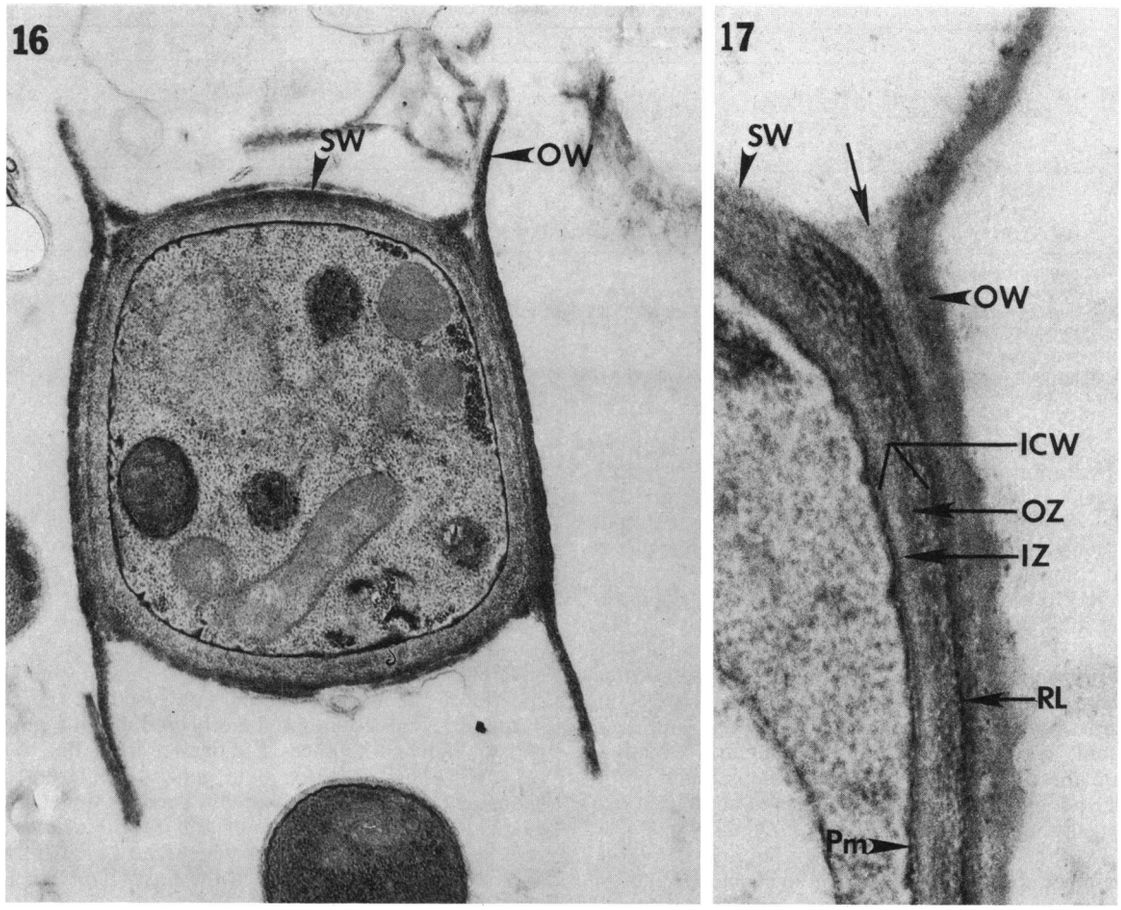


FIG. 16 and 17. Thin sections of enteroarthric conidia of *C. immitis* showing differentiation of wall layers. OW, outer wall layer which is continuous between adjacent conidium and degenerate cell and is homologous with original fertile hyphal wall; SW, septal walls of conidium; ICW, newly formed inner conidial wall composed of heterogeneous, fibrous outer zone (OZ) and more homgeneous inner zone (IZ); RL, rodlet layer; Pm, plasmalemma. Arrow locates wall material trapped between outer wall layer (OW) and rodlet layer (RL) which is released during the cell-shearing process. ×12,000 and 27,000, respectively.

One of the primary research activities of my laboratory has been the isolation, purification, and characterization of components of the conidial wall (79, 83, 92–94, 98, 99, 101), with emphasis on animal pathogens and those wall components which are capable of modulating host response (100). Similar approaches to studies of infection structures formed during fungal/plant interactions are under way in other laboratories (e.g., see reference 385; S. Kaminskyj and A. W. Day, Phytopathology **74**:833, 1984). Our attention has focused on the human respiratory pathogen *C. immitis*, since its conidium is the infectious cell type (123) and the conidial wall has been shown to play a pivotal role in early host response (93, 94; T. N. Kirkland, G. T. Cole, S. H. Sun, and J. Fierer, 9th Int. Congr. Int. Soc. Human Anim. Mycol., p. 3-3, 1985). Thin sections have revealed that the outer layer of the conidium is a sleeve of wall material (OW, Fig. 16 and 17), which represents the original wall of the fertile hypha (Fig. 1F and G). Scanning electron microscopy has shown that conidia may be smooth or coated with wartlike protuberances (93), while shadow-replica preparations reveal an amorphous, outer layer. Conidia subjected to the freeze-fracture (-etch) procedure (81, 306) have demonstrated fascicles of fibrous wall components called "rodlets" (205) located at the interface between the outer and inner wall layers. Closer examination of thin sections (Fig. 17) has disclosed that the rodlet layer (RL) is a thin but distinct, darkly stained zone adjacent to the inner conidial wall (ICW). The latter is composed of a heterogeneous outer zone (OZ, Fig. 17) in which dark- and light-stained fibrous elements are visible and an inner, more homogeneous fibrous zone (IZ). Rodlet fascicles are common components of the conidial envelope of Deuteromycetes (74, 96, 97, 194) as well as other fungal and bacterial propagules (46, 206, 284, 434, 439). Rodlets isolated from the surface of conidia are mainly proteinaceous (34, 194, 454) or lipoproteinaceous (92) and contribute to the hydrophobicity of the cell surface. This last feature of rodlet fascicles has been suggested to aid in conidial dissemination (31). The rodlet layer in some species is exposed on the surface of the conidium and fascicles are released when the hydrophobic cells are simply floated on distilled water (97). However, in the case of *C. immitis* the rodlets are enclosed by the outer wall layer (OCW, Fig. 17). This entire hydrophobic outer wall complex has been mechanically removed by a cell shearing technique (101) which involves use of a Ribi cell fractionator (Sorvall). The resultant sheared conidia are still intact and easily wettable (93). The residual inner wall layer swells slightly due to imbibition of water, but the cell remains viable. During the cell shearing

TABLE 1. Summary of chemical composition of arthroconidial wall fractions of *C. immitis*

Conidial wall fractions	% (dry wt)									
	Total neutral carbohydrate by:		Total hexoseamine	Peptides	Lipids			Ash	Phosphorus	Recovery
	GLC[a]	Anthrone[b]			Readily extractable	Bound	Other			
Outer wall	12.0[c]	(3.2)	1.7	49.8[d]	15.4	9.7	NM[e]	0.1		88.7
Soluble wall	31.6	(5.3)	0.6	28.5	7.4	5.2	20.0[f]	NM	NE[g]	93.3
Inner wall	32.3	(20.5)	21.9	27.4	4.5	12.9	NM	0.02		99.0

[a] GLC, Gas-liquid chromatography.
[b] Based on anthrone method. These values were not used to calculate recovery.
[c] Determined by summation of major monosaccharides identified by gas-liquid chromatography analysis.
[d] Determined by Kjeldahl method (see reference 93).
[e] NM, Not measurable.
[f] Lyophilized pigment component obtained from methanol-H_2O layer during isolation of readily extractable lipids from soluble wall fraction.
[g] NE, Not examined.

and wall hydration processes, certain soluble wall components are released to the aqueous medium. These and the particulate outer conidial wall components have been separated by centrifugation, and their chemical compositions have been compared (Tables 1 and 2). The sheared conidia are subjected to glass bead homogenization, and composition of the inner wall fraction has also been analyzed (93, 100). The most striking features of the outer conidial wall composition compared with the other two fractions shown in Tables 1 and 2 are low neutral carbohydrate (mannose is the predominant monosaccharide) and high protein and total lipid content. As expected from ultrastructural examinations, the highest percentage of hexosamine is found in the inner wall fraction and most is in the form of chitin (93). An unusual sugar component, identified as 3-*O*-methylmannose (329, 440), was detected in each fraction but is most prominent in the inner conidial wall preparation (Table 2). Interest in the occurrence of this monosaccharide originally stemmed from the fact that 3-*O*-methylated heteromannans have been identified in procaryotes (317; S. K. Maitra and C. E. Ballou, Fed. Proc. 33:1452, 1974), but no reports of this sugar in other fungi were published (441). A survey of the monosaccharide content of the cell walls in a range of pathogenic and nonpathogenic fungi was conducted, using gas chromatography/mass spectroscopy techniques (83). Only *C. immitis* and *Malbranchea dendritica* were shown to contain 3-*O*-methylmannose. The latter species has long been considered closely related to *C. immitis* (372), but is not capable of generating spherules or endospores in vivo (321). The uniqueness of 3-*O*-methylmannose in *C. immitis* compared with other fungal pathogens examined may be an asset for diagnosis of coccidioidomycosis, especially coccidioidal meningitis (244), by detection of minute quantities of the sugar in body fluids (272).

This comparative study of wall composition in *C. immitis* has underscored the degree of structural and chemical differentiation of its conidial wall. When the infectious propagule enters the respiratory tract of the host, it enlarges diametrically (Fig. 15M and Q), and by approximately 24 h postchallenge the inelastic outer wall layer of surviving conidia has ruptured. This results in exposure of the inner conidial wall and natural release of soluble components trapped below the hydrophobic outer layer of the cell envelope (94). It has been suggested that the changing spectra of chemical components released by the pathogen during early infection may be reflected in both quantitative and qualitative differences in antigen presentation to the host (93, 100). This, in turn could generate different host responses. *C. immitis* has, thereby, been used as a model for evaluating the significance of the fungal cell wall as a reservoir of macromolecules which can modulate humoral and cell-mediated immunity in the host (106, 107, 110–113, 258, 259, 271, 275–277, 427).

TABLE 2. Monosaccharide composition of arthroconidial wall fractions of *C. immitis*

Monosaccharide	Conidial wall fractions (%)[a]		
	Outer wall	Soluble wall	Inner wall
Mannose	64.6	30.3	45.8
Glucose	22.5	58.7	35.1
Galactose	11.5	7.9	7.1
3-*O*-Methylamannose	1.4	3.1	12.0

[a] Percentages of total neutral carbohydrate determined by gas-liquid chromatography.

Immunoreactive Wall Components of *Coccidioides*

The antigen content of various wall fractions of *C. immitis* has been analysed by immunoelectrophoresis techniques (14–16). Identification of specific antigens was based on a coccidioidin/anticoccidioidin reference system which had been developed earlier by Huppert and co-workers (229, 230). Coccidioidin (CDN), a skin test-active substance used for many years to survey populations for exposure to arthroconidia of *C. immitis* (124), was prepared as two separate products (228): a pooled, broth culture filtrate of several strains of *Coccidioides* mycelia (F fraction), and a toluene lysate of the washed, cellular retentate (L fraction). Anti-CDN (F plus L) was derived from a hyperimmunized burro and used in two-dimensional immunoelectrophoresis (IEP) to demonstrate at least 26 antigens in CDN (229, 230). The CDN/anti-CDN reference system was thereby established for monitoring antigenic content of various wall extracts of *C. immitis* (93, 111), as well as testing for cross-reactivity with extracts of other pathogenic and nonpathogenic fungi (83, 100, 230). Specific antigens were identified by the tandem two-dimensional IEP method of Cox et al. (111), or by including an internal precipitin peak (bovine serum albumin/anti-bovine serum albumin), and were designated by numbers according to the CDN/anti-CDN system (93). Antigens were also identified by the advancing-line IEP procedure (111, 340). The advancing-line IEP plate (Fig. 18) is composed of separately prepared agarose gels: a lower gel with barbital buffer (pH 8.6), an upper gel with precipitated and resolubilized immunoglobulins from burro anti-CDN

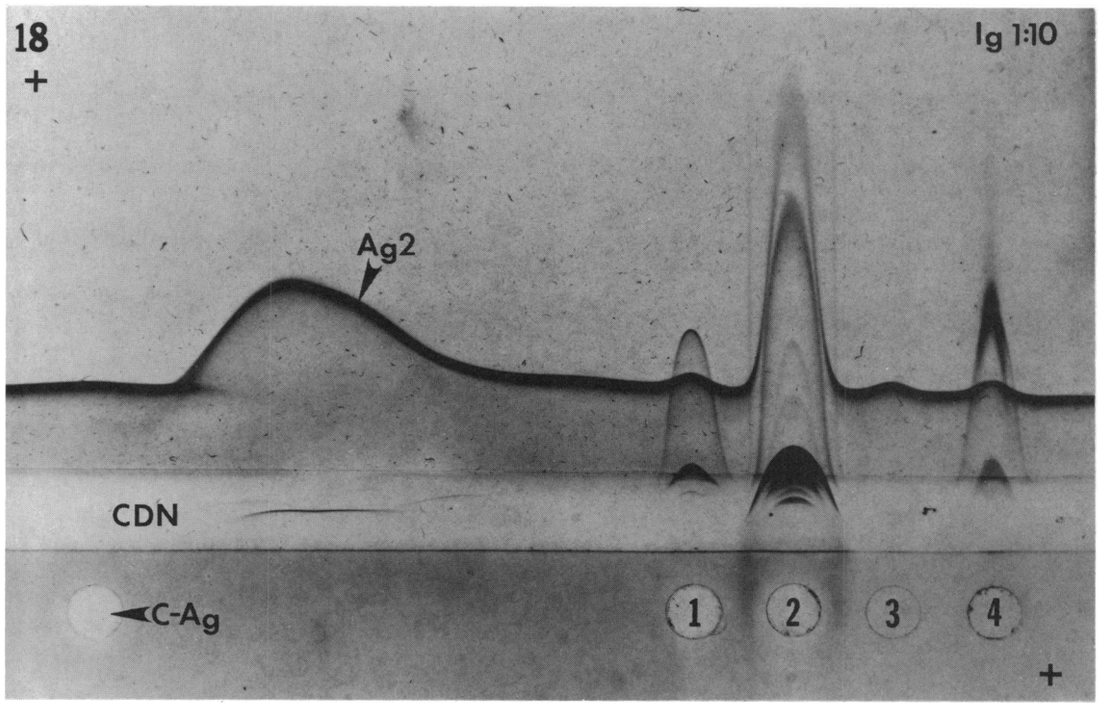


FIG. 18. Advancing-line IEP gel showing quantitative and qualitative differences in antigen composition between conidial wall and cytosol fractions placed in the anodal wells (1 to 4; phosphate-buffered saline extracts of outer wall, aqueous soluble wall, inner wall, and cytosol fractions, respectively). Note the large number of antigens (precipitin peaks) which develop above the aqueous soluble fraction (anodal well 2), which was derived from sheared conidia. C-Ag, Cathodal antigen composed of coccidioidin filtrate plus lysate concentrate at a dilution of 1:8 in electrophoresis buffer; CDN, same coccidioidin concentrate as above but at dilution of 1:128 in buffer and incorporated into the intermediate gel; Ag 2, antigen 2 (see text); Ig 1:10, immunoglobulin from burro anti-CDN serum diluted 1:10 in buffer. (+) indicate anodes and direction of migration in each dimension.

serum, and an intermediate gel containing the CDN reference antigen at a dilution of 1:128 in barbital buffer. The antigen placed in the cathodal well is also CDN, but at a lower dilution (i.e., 1:8) in electrophoresis buffer. The dilutions were determined optimal for development of a major antigen-antibody precipitin peak in the upper gel, the base of which is continuous with a precipitin line that advances from the intermediate gel (83, 111). The antigen has been identified as antigen 2 on the basis of comparison to the reference system (229).

In Fig. 18, phosphate-buffered saline extracts of the three isolated and lyophilized conidial wall fractions (cf. Tables 1 and 2), in addition to the cytosol fraction, were subjected to one-dimensional ("rocket") IEP in the advancing-line IEP plate. The intermediate gel contains the reference antigen (CDN, lot 89, F plus L; diluted 1:128) and the upper gel contains burro anti-CDN immunoglobulin diluted 1:10. This procedure provides a crude but rapid comparison of antigen content of multiple fractions. Both quantitative and qualitative differences in antigen composition of the conidial products are demonstrated. The most antigenic fraction is clearly the soluble material released during the cell shearing procedure. To determine whether this soluble fraction is composed of wall-derived antigens, cytosol-derived antigens, or both, rabbit antiserum was raised against the soluble, conidial components and then used in immunoelectron microscopy for locating the antibody-specific antigens (126). Polyclonal antibodies obtained from the rabbit antiserum were conjugated with gold particles (20 nm in diameter) and reacted with thin sections of intact arthroconidia (215). As control preparations, serial sections of the same cells were reacted with gold particles which were conjugated with antibody obtained from normal rabbit serum. Particles conjugated with the former were localized between the outer wall layer and plasmalemma (Fig. 20). Significant amounts of label were also found on the inner surface of the residual wall of the antolyzed cell (Fig. 19). Very little label was observed in the cytoplasm. These results support the contention that the soluble fraction (Tables 1 and 2; Fig. 18) is composed mainly of wall antigens derived from the intermediate zone between the outer and inner conidial wall layers (arrow in Fig. 17), as well as the inner wall layer itself.

Comparative studies of the immunoreactivity of selected wall and cytosol fractions of *C. immitis* have been conducted by using an immune T-cell proliferation assay (Kirkland et al., 9th Int. Congr. Int. Soc. Human Anim. Mycol., p. 3-3, 1985). Draining lymph node cells were obtained from BALB/c mice which had been immunized three times with attenuated spherules. The lymph node cells were cultured with or without antigen, and uptake of [^{3}H]thymidine was measured at 72 to 90 h as an estimate of cell proliferation. Table 3 shows the results of a typical experiment. The responses are expressed as Δ cpm (counts per minute with antigen − counts per minute without antigen). Standard errors were <10% of the mean. Three concentrations of each antigen were tested. Results of only the most reactive antigen concentration are presented. These data indicate that intact spherules are more stimulatory for lymph node cell proliferation than arthroconidia, which is consistent with reports of earlier investigators (274). However, the fraction

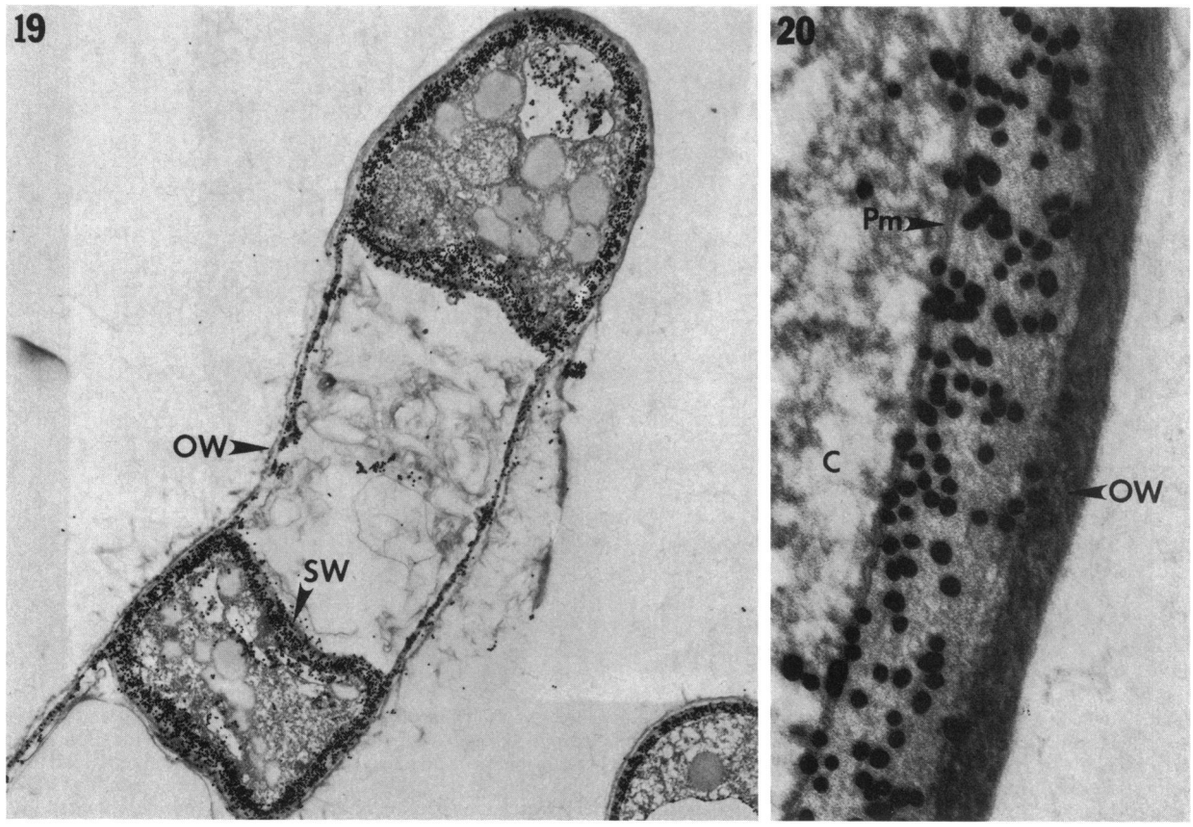


FIG. 19 and 20. Thin sections of arthroconidia which were reacted with polyclonal antibodies conjugated to 20-nm colloidal gold particles. The polyclonal antibodies were obtained from rabbits immunized with aqueous soluble components derived from sheared conidia (cf. Fig. 18, Tables 1 to 3). Antiserum dilutions in buffer were 1:10,000 (Fig. 19) and 1:100,000 (Fig. 20). Note few gold particles present on outer conidial wall (OW) and cytoplasm (C) and concentration of particles on inner wall layers and plasmalemma (Pm) in Fig. 20. Also note presence of gold particles on inner surface of residual outer wall (OW) of degenerate cell and septal walls of conidia (SW) in Fig. 19. ×9,000, and 50,000, respectively.

containing soluble conidial wall components is about six times more stimulatory than intact conidia and the most stimulatory of any of the fractions so far tested. The immunoreactive macromolecules may be masked in the intact conidium and are released when the outer, hydrophobic wall layer is removed. Preliminary investigations have been conducted on the immunoprotective capacity of the soluble wall components (plus adjuvant) administered subcutaneously to BALB/c mice prior to intranasal challenge with a lethal dose of viable arthroconidia. Our results (unpublished) have shown that the soluble wall components elicit a delayed-type hypersensitivity response in immune animals and provide good immunoprotection, which is at least equal to the immunoprotective capacity of previously examined fractions (271, 274). Evidence is available from studies of other host-pathogen relationships that antigen-specific proliferating T cells can protect animals against infection (245, 282). Since an important component of the immunological control of coccidioidal infections is T-cell sensitization (30), it follows that the soluble conidial wall fraction is the source of a potential vaccine against coccidioidomycosis. Efforts are under way to identify and purify the immunoreactive components of the soluble conidial wall fractions (99), using polyclonal and monoclonal antibodies in immunoadsorption procedures (348). An additional, exciting result of current studies of the isolated outer conidial wall layer is that components are also present which suppress immune lymph node T-cell proliferation (T. N. Kirkland, G. T. Cole, and S. H. Sun, unpublished data). The suppressive factors can be extracted from the hydrophobic wall fraction by using freshly distilled methanol. The pervaporated methanol fraction lacks antigens which can be detected by the CDN/anti-CDN reference system. In view of earlier reports that a significant percentage of arthroconidia are able to survive in the presence of phagocytes in vitro (29, 123), this discovery has interesting implications which require careful examina-

TABLE 3. Immune lymph node T-cell proliferation[a]

Antigen	Mean Δcpm[b]	
	Arthoconidia[c]	Spherules[c]
Intact cells	18,462	51,901
Soluble outer wall obtained after cell shearing	112,600	26,853
Cytosol	27,275	15,179

[a] Lymph node cells obtained from BALB/c mice immunized with attenuated spherules of *C. immitis*.

[b] Counts per minute of [^{3}H]thymidine-labeled lymph node cells exposed to antigen − counts per minute without antigen.

[c] Cell type from which antigens are derived.

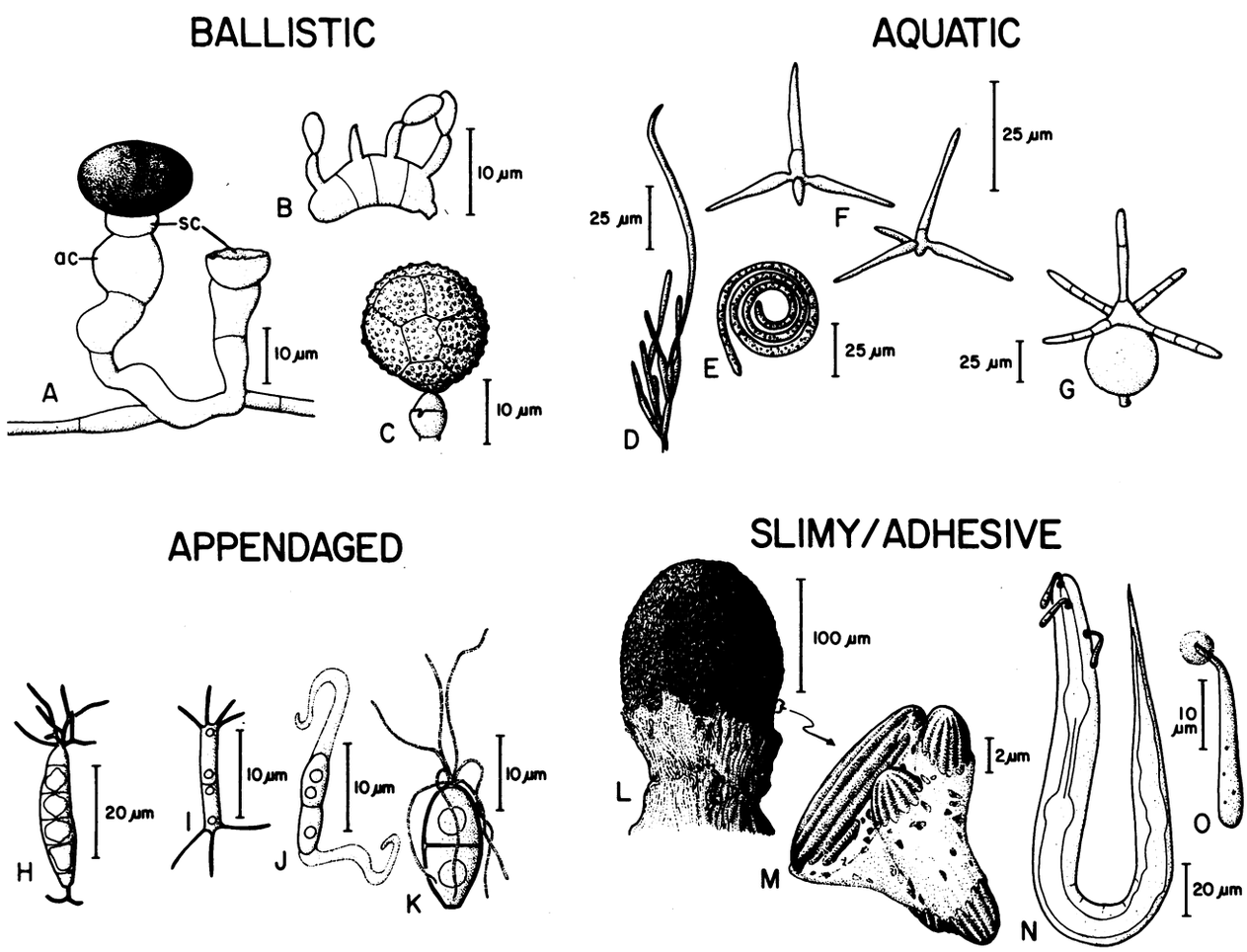


FIG. 21. Examples of conidial morphology and adaptations for dispersal. A, *Nigrospora* sp. (after reference 432); B, *Dacrymyces* sp.; C, *Epicoccum nigrum* (after reference 432); D, *Filosporella* sp.; E, *Helicomyces* sp.; F, *Triscelophorus* sp. (after reference 61); G, *Orbimyces spectabilis*; H, *Pestalotia pezizoides* (after reference 400); I, *Dwayalomella* sp. (after reference 314); J, *Discosiella* sp. (after reference 311); K, *Comatospora* sp. (after reference 311); L, M, Sporodochium and conidia of *Myrothecium* sp.; N, O, *Meria coniospora* attached to nematode (N) (after reference 432).

tion and comparison to the immunomodulating activity of fractions obtained from other pathogenic fungi (312).

CONIDIAL FORM AND ADAPTATION

The size, density, and surface topography of airborne conidia are important considerations in studies of the distribution of potentially infectious propagules and aeroallergens within the mammalian respiratory tract (13, 97, 167). Conidia in the range of 2 to 5 μm can pass down through the trachea, bronchi, and bronchioles and reach the alveoli. The arthroconidia of *C. immitis*, which measure 3 to 6 by 2 to 4 μm, penetrate to the tiny air sacs where they encounter alveolar macrophages (123). In addition to its protective and possible immunosuppressive functions, the dry hydrophobic envelope of these and other airborne conidia produced by pathogenic and allergenic species is an important adaptive feature for efficiency of dissemination outside the host (31, 97), as well as within the moist environment of the respiratory tract.

The source of most airborne conidia is vegetation, both living and decomposing, which resides upon or above the soil (19, 167, 269). The soil itself is an immense reservoir of conidial fungi, some of which grow and sporulate in situ and contribute to the breakdown of organic debris. Other species are transients, sporulating on exposed substrates and passively dispersed in air currents. Dense clouds of conidia may be transported over long distances, some of which colonize new subtrates on the surface of the soil. A few species have supplemented passive air current dissemination with mechanisms of forcible discharge of their conidia (Fig. 21A to C). Webster (429) has recorded projections of the large, pigmented conidia of *Nigrospora sphaerica* (Fig. 21A) over vertical and horizontal distances of 2 and 6.7 cm, respectively. A narrow channel provides for cytoplasmic continuity between the ampulliform conidiogenous cell (ac) and young, developing conidium. A supporting collar (sc) holds the conidium in position at the apex of the fertile cell. The latter is thick walled and apparently establishes an internal hydrostatic pressure as the conidium reaches maturity. When the fungus is subjected to desiccating conditions, the pressure within the conidiogenous cell is released by expulsion of its cytoplasmic contents through the narrow channel. This results in separation of the conidium from the supporting collar and its propulsion into the air (429, 432). The

surface of the conidium is sticky and adheres to the substrate with which it impacts. *Nigrospora sphaerica* is an economically important parasite of grasses, cereals, and other monocotyledonous plants (131, 133). The ballistoconidia provide for effective colonization of aerial plant parts. A large number of Basidiomycetes also produce ballistoconidia which arise directly from seceded basidiospores (Fig. 21B). A single conidium is commonly borne assymetrically at the apex of a peg or denticle and is forcibly discharged in apparently the same manner as many basidiospores (255). One mechanism of violent spore release which is recognized among basidiomycetous fungi involves the abrupt "rounding off" of the septal wall at the apex of the supporting peg (sterigma) adjacent to the rigid basal septum of the spore (436). A similar process of discharge occurs in *Epicoccum nigrum* (Fig. 21C), except that the two apposing septal wall layers simultaneously round off, resulting in projection of the conidium (235, 431). As in *Nigrospora* spp., a marked reduction in humidity is considered to trigger conidial release (296, 432).

Evolution of conidial form among the aquatic Hyphomycetes has resulted in two easily recognized shapes: the sigmoid or helicoid conidium (Fig. 21D and E), and the tetraradiate or branched conidium (Fig. 21F and G). Most of these fungi are found in freshwater habitats, occurring abundantly in babbling brooks and well-aerated lakes as saprobes on leaves and twigs. Conidia are often found in foam which collects around small barriers or in backwaters near turbulent runs in many streams (433). Conidial production, liberation, transport, and eventual deposition in these aquatic species occur primarily below water (235–238). The advantages of the tetraradiate shape (Fig. 21F) are twofold: it provides for greater buoyancy and, therefore, more effective dispersal in water, and it serves as an anchor by impacting on underwater objects (234, 237). This latter feature would be especially important in a turbulent stream. Some experimental support for these functional concepts has been provided (430, 433). The trapping efficiency of bubbles in the persistent foam of streams has been shown to be related to conidial shape (238, 239). The tetraradiate conidia of *Articulospora tetracladia* are trapped about 30 times more efficiently than the ovoid cells of yeasts. Ingold (238) has also suggested that rising bubbles of foam which burst at the surface may further contribute to dispersal by throwing the trapped conidia into the air. Variations in the basic tetraradiate shape are recognized, such as the bulbous conidia of the marine Hyphomycete *Orbimyces spectabilis* (Fig. 21G). The functional significance of the sigmoid and helicoid shapes among aquatic fungi is not clear. Certain sigmoid conidia are capable of attaching to submerged substrates by their tips (433), while helicoid conidia seem to have the advantage of greater buoyancy. Webster and Descals (433) distinguished between strictly aquatic fungi and aeroaquatic species. The latter are found in stagnant ponds, ditches, or slow-running streams where they grow vegetatively on submerged leaves and twigs, but sporulate only when the substrate is exposed to air. The conidia are dispersed as the substrate is again submerged and demonstrate elaborate helicoid, multicellular, and appendaged forms. The flat, tightly coiled conidia of *Helicomyces* spp. are dry when formed, but are hygroscopic and frequently uncoil when immersed in water (163). On the other hand, the three-dimensional, barrel-shaped conidia formed by the tight-winding of a spiral hypha in *Helicodendron* spp. are virtually unsinkable due to air pockets that are trapped as the conidia develop at the air-water interface (433).

Many of the conidia produced by Coelomycetes are characterized by secondary structures referred to as appendages, pedicels, setae, and cilia. Two basic types of appendages are recognized (315): cellular, originating as tubular extensions of the conidium body (Fig. 21H and I); and extracellular, arising without cytoplasmic continuity with the conidium body (Fig. 21J and K). Both bipolar and unipolar appendages are formed, some of which are elaborately branched. Extracellular appendages are considered to be mucilaginous in nature and originate from a sheath that surrounds the developing conidium. The details of such appendage formation are unknown, but a high degree of consistency in their morphology is demonstrated by a particular taxon which, thereby, provides a useful character for identification of these fungi (315). Coelomycete conidia are largely produced in slimy masses and not forcibly discharged but dispersed by water and foraging insects (400). Appendages probably represent adaptations for insect dispersal but may also contribute to buoyancy and attachment to substrates during dissemination.

Certain members of the conidial fungi produce their propagules in a slimy mass arranged in a column above an aggregation of conidiogenous cells (i.e., sporodochium; Fig. 21L). The mucilaginous substance appears to be released during conidium formation and effectively binds the cells together in great numbers (Fig. 21M). In some of the coelomycetous forms, the slimy conidia emerge from the interior of the fruiting body (pycnidium) through a small pore (ostiole), forming a tendril-like mass of cells called a cirrus (3). These dense clusters of conidia can be formed under optimal conditions during just a few hours. The conidial masses readily disperse in a droplet of water or may be transported intact on the appendages of insects. Conidia produced by some of the predacious Hyphomycetes, such as *Meria coniospora* which is an endoparasite of nematodes, are equipped with mucilage-coated, sticky tips (Fig. 21N). The conidia become attached to the cuticle of the host and, upon germination, penetrate into the body cavity, eventually filling it with hyphae (432).

INDUCTION OF CONIDIOGENESIS

Environmental Factors

It has long been recognized that environmental factors are capable of checking vegetative fungal growth and initiating differentiation of reproductive structures (257). In the case of filamentous forms, when the rate of nutrient uptake by the mycelium and rate of utilization are constant, the organism is considered to be showing balanced growth and normally maintains its vegetative morphology (49). Under these conditions, fungal development is regulated by inherent genomic characters rather than by environmental factors (379). When limitations result in an unbalanced system, metabolic alterations occur which may lead to differentiation of conidium-producing structures (378). Environmental conditions which induce and sustain conidiation are apparently more limited than those permitting mycelial growth (197). The two processes may be antagonistic, although not incompatible, since alternate metabolic pathways are suggested to be in operation. Smith (378) proposed that "vegetative growth and sporulation should be considered as cellular processes which are competing for limiting metabolic intermediates rather than as mutually exclusive phenomena. If vegetative growth and sporulation do not . . . occur simultaneously, and are separated by definite metabolic shifts, the point of change

may be associated with the limitation of vegetative growth due to nutrient exhaustion or to some other environmentally controlled limiting process." Conidiogenesis is the result of inherent genetic competence responding to specific environmental factors. These responses, in turn, promote changes at the cellular level, giving rise to new metabolic patterns (379, 409, 412).

To critically examine the influence of environmental factors on asexual reproduction in the conidial fungi, the use of simple and complex fermentor systems has been introduced (378). These have permitted investigations of how specific environmental parameters such as aeration, temperature, pH, nutrient type, and concentration affect conidiation in submerged cultivation (379). Under carefully manipulated fermentor conditions, synchronous control of conidiation in certain species has been achieved (9, 10). An abbreviated developmental process occurs, referred to as microcycle conidiation (379). The short germ tubes of conidia give rise directly to conidiogenous cells without an intervening phase of mycelial growth. An added advantage of such synchronized cultures is that they permit sharp separation of developmental phases during medium replacement (10) and thus provide insights into the biochemical changes accompanying selected events of conidiation (379). Several imperfect fungi have been examined by using microcycle conidiation techniques, including *Aspergillus niger* (9–11), *N. crassa* (109, 356), *Penicillium urticae* (369), *Paecilomyces variotii* (8), *G. candidum* (7, 324), *Trichoderma harzianum* (462), and *Acremonium diospyri* (365).

A. niger has proved to be a particularly suitable model for examining the influence of temperature and nutrient manipulation of microcycle cultures on the induction of conidiation (7). Conidia are first incubated in a defined liquid medium maintained in a shaking incubator at a critical supraoptimal temperature (44°C) for 24 h. During this period, the conidia enlarge (spherical growth) to 20 to 24 μm in diameter, and germination is inhibited. In the absence of this temperature limitation, the nutrients present in the growth medium would support vegetative growth. The enlarged parent conidium (giant cell) is thick walled and multinucleate (116; S. G. Deans, Ph.D. dissertation, University of Strathclyde, Glasgow, Scotland, 1978). When the incubation temperature is reduced to 30°C, one or more fertile hyphae (conidiophores) emerge from the giant cell, each supporting a cluster of fertile cells (conidiogenous cells) at its swollen apex (vesicle). The size and structural complexity of the conidial apparatus under these growth conditions is reduced compared with subaerial conidiation (10, 380). However, the conidia are similar in size and capable of repeating the cycle or, alternatively, giving rise to vegetative hyphae under appropriate environmental conditions. Since a single giant cell ultimately gives rise to a significant biomass in microcycle culture, one can assume that the reproductive structure is continuously taking up nutrients from the media rather than simply utilizing stored reserves in the parental cell (7). The microcycle system, therefore, consists of two stages: in stage 1, at elevated temperature, conidium enlargement and hyphal restriction occur, and in stage 2, at lower temperature and in the presence of appropriate nutrients, conidiation occurs. The temperature regime, duration of each stage, and nutritional status of the medium are species specific (379). For example, the temperature difference between stages 1 and 2 for *N. crassa* is 21 (109, 356), that for *Paecilomyces variotii* is 8 (8), and that for *Penicillium urticae* is only 2 (369), while for *A. niger* the difference is 14.

In addition to the influence of temperature, manipulation of assimilable nitrogen and carbon sources in the medium are also key features of the microcycle induction process (172). Stage 1 in *A. niger* is characterized by giant cell growth in a medium which would support vegetative mycelial development if not inhibited by the restrictive temperature (379). The medium contains both N and C sources, but N is the limiting nutrient (378). Induction of conidiophore development occurs when exogenous N is exhausted but presence of the C source (glucose) is maintained. The medium is then replaced with one containing an N source and citrate as the C source, which induces vesicle and conidiogenous cell (phialide) formation. Induction of conidium formation is then achieved by transfer into a medium with glucose as the C source and nitrate as the N source.

Carbon dioxide was originally suggested to contribute to the induction of giant cell development and inhibition of germ tube formation during stage 1 of microcycle conidiation in *A. niger* (265, 379). However, subsequent studies have failed to confirm these observations. Light has long been known to influence development of conidial fungi (270) and certain species have been categorized as "diurnal sporulators" (e.g., *Alternaria dauchi*, *Aspergillus tomato*, and *Stemphylium botryosum*). Kumagai (266) has pointed out that photoconidiogenesis in these fungi has two distinct phases; an "inductive phase" stimulated by near ultraviolet light, which leads to formation of conidiophores and conidiogenous cells, and a "terminal phase" inhibited by near-ultraviolet or blue light which results in conidium formation. A photoreceptor system (mycochrome) is apparently involved in a blue and near-ultraviolet photoreaction which in turn plays an important role in photocontrol of conidial development. In *A. tomato*, a blue light-absorbing pigment (P_B) and a near-ultraviolet-absorbing pigment (P_{NUV}) are involved in the photoreaction. Apparently, P_{NUV}-mediated photoreductions of P_B and cytochrome *c* occur under anaerobic and aerobic conditions (266). Light-induced conidiation has also been examined in *A. ornatus* (207) and *A. giganteus* (140, 463). Light has been shown in the latter species to cause an increase in cyclic adenosine 5′-triphosphate level and concomitant increase in phosphodiesterase activity within the elongating conidiophores. Cyclic nucleotides apparently have a regulatory effect on photomorphogenesis in *A. giganteus*. Hill (207) suggested that light may affect glucose assimilation and thereby regulate conidium formation. Under conditions of continuous light, inhibition of glucose uptake and phosphorylation precedes conidiation. The mechanism of regulation of cyclic adenosine 5′-monophosphate metabolism and nature of participation of cyclic adenosine 5′-monophosphate in glucose metabolism of conidial fungi requires further investigation (463). Although temperature and nutrient limitation are of primary importance in the induction of conidiation, a spectrum of still unexplored environmental factors may also play important roles in the induction process by influencing essential growth-limiting reactions (378).

Biochemical Events

Conidiogenesis seems to be controlled by both ordered events associated with transcription and translation (i.e., enzyme control) and substrate and product concentrations involving feedback inhibition or stimulation (i.e., intermediate control) (378). These two systems are apparently closely integrated, and no single controlling step exists but rather an ordered sequence(s) of steps. Wall morphogenesis and pat-

terns of cell development are intimately related. Thus, analyses of mural enzyme activities during microcycle conidiation may provide important clues about mechanisms which regulate conidial differentiation. The major wall components of *A. niger* are chitin, α- and β-glucans, and galactomannan polymers, plus protein and lipid (98, 379). The corresponding enzymes involved in synthesis and degradation of these wall components include glucan synthetase, α- and β-glucanase, chitin synthetase, and chitinase. These enzymes have been subcellularly localized and monitored during microcycle conidiation (379). During early development of the giant cell of *A. niger*, α-1,3-glucan was elaborated in the cell wall as well as an alternating α-1,3- and α-1,4-polymer, commonly referred to as nigeran (38). The latter, at least in regenerating protoplasts, is incorporated as a secondary wall polymer after synthesis of other wall polymers or attainment of a particular cell shape or both (122). During microcycle conidiation, α-1,3-glucan and its synthetic enzyme decreased in concentration toward the end of stage 1, while nigeran remained firmly constant and α-glucanase showed a marked increase. This increase in lytic enzyme activity has been suggested (379) to be due to reutilization of some of the excess α-glucan moieties or rechanneling of glucose monomers at the end of stage 1 in preparation for the initiation of stage 2. β-1,3-Glucan and β-glucan synthetase increase throughout the microcycle. β-Glucans may serve as a cementing matrix in fungal cell walls, binding together chitin microfibrils and other polymers (12). The lytic enzyme β-glucanase never exceeded 20% of the corresponding synthetase during giant cell formation. Thus, β-glucans are conserved, not reutilized like α-glucans, and apparently contribute to the structural framework of the giant cell wall. Chitin levels similarly increased during stage 1; chitin synthetase concomitantly increased and then remained elevated, and chitinase remained low. Chitin also contributes to the wall rigidity and cell shape. Close examination of chitin synthetase activity during microcycle conidiation (379) has revealed that the enzyme isolated from giant cells was primarily in its zymogenic form and demonstrated the capacity for prolonged activity, while chitin synthetase isolated from stage 2 was active and short-lived. Such differences are perhaps reflected in the thickened wall of the giant cell and the contrasting thinner wall which encompasses the elongating conidiophore (379).

By using a selection of metabolic inhibitors, it has been possible to obtain information on the sequence of production of RNA and protein fractions associated with induction of microcycle conidiation in *A. niger* (7, 117, 379). It appears that synthesis of the essential macromolecules is completed by 15 to 16 h in stage 1, at which time conidiation competence has been established in the giant cells. However, if these cells are transferred to the permissive temperature (30°C) prior to 20 to 22 h of incubation at 44°C, a marked reduction in conidiophore development and poor conidiation is observed. Allermann et al. (7) have suggested, that although competence is achieved 15 to 20 h after induction of giant cell growth, "expression of conidiation is restricted by thermal inhibition of some part of the conidiation process." When giant cells were exposed to actinomycin D (20 μg/ml) at 0 to 6 h after induction, their growth rate was reduced but not inhibited. At 30°C the cells were capable of germination but formed vegetative hyphae rather than conidiophores (379). With various inhibitors, it was shown that a minimum giant cell diameter of about 15 to 16 μm was necessary for microcycle conidiation (117). If actinomycin D was added at progressively later times postinduction in stage 1, an increasing percentage of giant cells achieved conidiation competence. On the basis of these studies, Smith et al. (379) suggested that messenger RNA formation is essential for conidiophore and conidium development in microcycle cultures, and transcription occurs during the early period of stage 1. When used at 20 μg/ml, actinomycin D may not destroy preexisting messenger RNA. The authors proposed that formation of new messenger RNAs in stage 1 is necessary for conidiation but not for vegetative growth.

Experimental Mutants

One of the major contributions of genetics to an understanding of conidium and conidiogenous cell development lies in the provision of well-defined, morphological mutants (68). Single mutations, confined to single genes, can yield valuable information on related biochemical and morphological alterations and thereby establish causal relationships. A large pool of experimental mutants are now available among the conidial fungi and, in particular, among species of *Aspergillus*, *Penicillium*, and *Neurospora*. Based on comparisons between the frequency of conidiation mutants and frequency of auxotrophs or other known mutants, Martinelli and Clutterbuck (289) established that 45 to 150 genes are specifically concerned with conidiogenesis in *A. nidulans*. The authors classified the conidiation mutants according to the stage of development affected as follows: colonial mutants, tactical (morphogenetic) mutants, mutants defective at support loci, and mutants defective at auxillary loci. The largest class of mutants (85% of total) are those which show poor colony growth rate and secondarily demonstrate poor conidiation as a result of restricted hyphal growth. Since these colonial mutants probably carry a general defect shared by vegetative mycelial growth and conidiation, and are distinct from specific aconidial mutants, they were excluded from the estimate of numbers of loci cited above.

Strategic mutants, which are blocked prior to initiation of conidiogenesis, are exemplified by *Penicillium baarnense* (67, 68). The wild type is capable of moderate conidiation and produces numerous sexual fruiting bodies. Three types of strategic mutants are recognized for this species: sterile mycelial mutants defective at both conidiation and sexual reproduction loci, profuse conidiating mutants blocked before initiation of sexual reproduction, and abortive sexual mutants. These mutants illustrate that alternative pathways leading to different morphogenetic processes can be distinguished in conidial fungi. Strategic mutants should provide important information on the differentiation of biochemical events leading to induction of either vegetative growth or conidiation.

Tactical or morphogenetic mutants are blocked in the process of conidial development. Such mutants undergo morphological changes which signal the onset of conidiogenesis but fail to complete the developmental process and do not move on to the next stage. As a result, growth continues by maintenance or repetition of the previous morphogenetic step. Several interesting mutants of *Penicillium claviforme* have been described which are included in this category (460). For example, in *BG* mutants of this fungus the conidiogenous cells (phialides) usually produce only one indehiscent, thick-walled conidium rather than a basipetal succession of conidia characteristic of phialidic development (Fig. 14B). The single, apical conidium is enucleate and the phialide is uninucleate. Apparently both wall formation, associated with repetition of conidium for-

mation (Fig. 14B), and nuclear division, which normally occurs within the phialide (Fig. 15B to E), are blocked. Other tactical mutants include *BW* in *Penicillium claviforme* (460) and the equivalent in *A. nidulans*, referred to as *abacus* mutants (67, 68). In both cases the phenotype is characterized by acropetal proliferation of the phialide (see Fig. 1N) without formation of conidia. It appears that wall differentiation associated with basipetal formation of multiple conidia at the phialide apex (see Fig. 14A) is blocked, and instead the phialide wall remains intact and proliferates at its apex to form a new phialide, resulting in formation of an acropetal chain of sterile conidiogenous cells. Wild-type strains of *N. crassa* give rise to blastic conidia in acropetal chains which then disarticulate after lysis and mechanical separation of septa between adjacent cells of the chain (see Fig. 13A; septa of *N. crassa* are uniperforate). The *csp* mutants of this fungus (413) are blocked at the conidial separation stage, apparently because of the absence of a wall lytic enzyme activity which maps at two loci (68, 370). These and many other tactical (morphogenetic) mutants provide the opportunity to analyze pivotal events, particularly those associated with wall differentiation and the nuclear cycle, which regulate blastic and thallic development in the conidial fungi.

Mutations at support loci reveal ill-defined defects in the conidiophores and conidiogenous cells which result in reduced conidiation (67, 68). Apparently most of these mutants are temperature sensitive and slow growing. The latter feature reinforces the suggestion that many common genes regulate metabolic processes in both vegetative and conidiation phases of the fungus (cf. colonial mutants [289]).

Mutations at auxillary loci also demonstrate partially defective conidiation, but the phenotypes are better defined than those resulting from defects at support loci (67, 68). For example, Selitrennikoff (Neurospora Newsl. **23**:23, 1976) identified an easily wettable or *eas* mutant of *N. crassa* which lacks rodlet fascicles on the surface of the conidial wall (see Fig. 3) and is poorly dispersed in air currents. The wild-type strain produces hydrophobic conidia with an intact rodlet layer (31). Although rodlet production is not essential for conidiation, it is an important aspect of the reproductive capacity of the fungus. Phenol oxidase production in *A. nidulans* has been examined with the aid of ivory conidiophore mutants and yellow conidial mutants, both of which are morphologically normal (66, 67). It was determined that cresolase is localized in conidiophores and laccase is localized in conidia. Each is concerned with formation of a separate pigment and has a substrate specificity separate from each other and from mycelial phenol oxidases. The specific enzyme is poorly produced at the appropriate developmental stage in each mutant and neither is produced in bristle mutants which fail to reach these stages of conidiation.

The majority of conidiation mutants have defects at support or auxillary loci (67, 68). Those mutants which have been clearly identified with defects at morphogenetic loci demonstrate that the relevant genes not only regulate patterns of activities of enzymes and other proteins that are unique to the developmental event, but also may coordinate activities of these same products at other stages of the life cycle. Clutterbuck (68) has suggested that "the whole picture is one, if not of economy in numbers of genes involved, at least of opportunism in the use of existing genes in a variety of conditions." On the other hand, evidence is available from investigations of *A. nidulans* mutants that some genes have evolved that are specifically associated with conidiation (457). Results of nutritional experiments with a *trpC* mutant have indicated that developmental regulation of *trpC* messenger RNA levels may be related to a high requirement for tryptophan or a compound derived from tryptophan during conidiophore development and conidium formation. In contrast, only low concentrations of tryptophan are required to support normal hyphal growth of the *trpC* mutant. The *trpC* gene from *A. nidulans* has been cloned by complementation of *Escherichia coli*, and its expression (as polyadenylated RNA) has been investigated under different conditions of growth and development (457).

SUMMARY

The conidial fungi demonstrate a broad range of morphogenetic complexity, from simple yeast budding and terminal, holoblastic conidium ontogeny to development of a plurality of conidia from elaborately differentiated conidiogenous cells and formation of structurally complex fruiting bodies (i.e., conidiomata) which totally or partially enclose the conidia and conidium-forming cells. This last mode of development, which is characteristic of many Coelomycetes and a few Hyphomycetes, was not examined in this review and represents a largely unexplored area of differentiation in this group of fungi (78, 80, 119, 315, 400). Conidiomata (singular, conidioma) is a term which encompasses all specialized, multihyphal, conidium-bearing structures, including acervuli, pycnidia, sporodochia, synnemata, and intermediate types of fruiting bodies (254, 315). In addition to their fascination as unusual examples of cell differentiation among the conidial fungi, a large percentage of the Coelomycetes are parasites of crop plants around the world. Concerted efforts are warranted in deriving a better understanding of the mechanisms of conidiomatal development both on natural substrate and in pure culture (120, 401).

The septate hypha is a fundamental element from which reproductive structures in the Hyphomycetes are derived. In most examples of blastic and thallic development, the fertile hyphal tip is the site of pivotal events which can lead directly or indirectly to conidium differentiation. Much information has been gathered on ultrastructural features of the hyphal tip and morphogenetic controls of polarized hyphal growth. Such studies have contributed significantly to formulation of the present concepts of conidium ontogeny. Similarly, investigations of septum formation in vegetative hyphae have contributed to our understanding of the structure, development, and functions of conidial septa. Delimitation of blastic and thallic conidia and their eventual secession from the parental cell depends on septum differentiation. Temporal and perhaps spatial control of septation appear to be closely allied to karyological events within the conidiogenous cell and conidium. Several excellent models are available for investigating this critical aspect of conidiogenesis, including phialidic development in *Gliomastix murorum* and thallic-arthric development in *G. candidum* and *C. immitis*.

Differentiation of the cell wall, including development or operation or both of all relevant cytological and biochemical machinery, is a fundamental aspect of conidiogenesis (23). Interest in the composition of the conidial and hyphal wall of medically important fungi as well as plant pathogens has recently focussed on the outermost surface layer and the nature of its interaction with host tissues. The dry, hydrophobic outer conidial wall layer, which is an important adaptation for air dissemination in the majority of terrestrial species, is mainly the result of differentiation of a distinct proteinaceous or lipoproteinaceous zone referred to as the

rodlet layer. Much of the success of adaptation of conidial fungi to a plethora of different habitats is associated with evolution of different patterns of wall morphogenesis.

Turian (412) defined morphogenesis as "the development of an organism to its specific form." The author has also pointed out that an essential aspect of differentiation is polarity (37, 50, 374), which is dependent on specific protoplasmic structures providing the necessary physical asymmetry (50). This, in turn, provides for the origin of spatial patterns of differentiation, which are typical of conidial fungi as well as many other eucaryotes. The ultimate analysis of gene regulation of spatial differentiation requires simple, well-defined models which can be easily manipulated. A few examples of such experimental models of cell differentiation in the conidial fungi have been described in this review.

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